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4-HYDROXYQUINOLIN-2-ONES. 45*. SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF N-SUBSTITUTED 1H-4-HYDROXY-2-OXOQUINOLINE-3-ACETIC ACID AMIDES

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A preparative method is proposed for obtaining N-substituted 1H-4-hydroxy-2-oxoquinoline-3-acetic acid amides. X-Ray diffraction analysis of one of the synthesized compounds has been carried out. The effect of the obtained substances on thyroid gland function has been studied.

Keywords: amides, tetrahydrofuroquinoline, quinoline-3-acetic acid, X-ray diffraction analysis, thyroid-stimulating activity.

During a study of different approaches to the synthesis of 1H-3-(coumarin-3-yl)-4-hydroxy-2-oxoquinolines one of the side products reported by us was 1H-4-hydroxy-2-oxoquinoline-3-acetic acid piperidylamide. In experiments on animals it showed a high antithyroid activity, exceeding that of mercazole which is used in medicinal practice [2].

Continuing our investigations in this area we have now developed a preparative method for obtaining N-substituted 1H-4-hydroxy-2-oxoquinoline-3-acetic acid amides (**1**) *via* acylation of the corresponding amines with 2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-2,4-dione (**2**) in refluxing pyridine. Synthesis of anhydride **2** can be brought about in a number of ways, in particular by treatment of 1H-4-hydroxy-2-oxoquinoline-3-acetic acid (**3**) with thionyl chloride or N,N'-dicyclohexylcarbodiimide (in the first case chloride of acid **3** was not separated). In these conditions acetic anhydride gives only 4-O-acetyl derivative **4**. Although anhydride **2** is indeed formed by cautious heating of acid **3** to a temperature around 300°C, this method does not have a preparative value. The optimum, both in terms of yield and with respect to costing of time and the condensing agents is in our view the thermolysis of the simplest alkyl esters of 1H-4-hydroxy-2-oxoquinoline-3-acetic acid (**5**). These are, moreover, more readily available in the pure state than is acid **4**. Being a rather strong acylating agent, anhydride **2** readily acylates primary and secondary amines including those which are sterically hindered (e.g. diisopropylamine) to give the corresponding amides **1** (see Table 1). In the case of optically active amines, racemization was not observed (amides **1a,b**).

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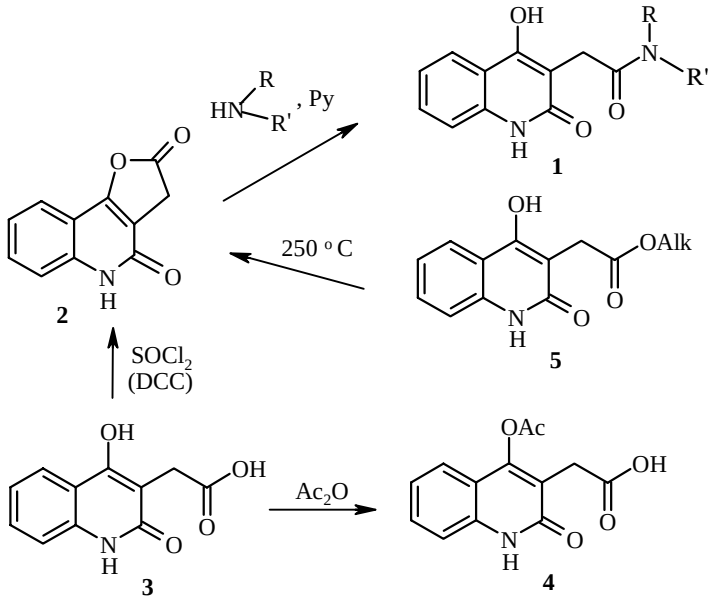

1 a R = *S*(–)CH(CH$_3$)C$_6$H$_5$, R' = H; **b** R = *R*(+)CH(CH$_3$)C$_6$H$_5$, R' = H;
c R = (±)CH(CH$_3$)C$_6$H$_5$, R' = H; **d** R = C$_6$H$_5$, R' = CH$_3$;
e R = R' = C$_2$H$_5$; **f** R = R' = *i*-C$_3$H$_7$; **g** R = R' = C$_4$H$_9$; **h** R = R' = *i*-C$_5$H$_{11}$;
i R = R' = CH$_2$C$_6$H$_5$; **j** morpholyl

According to ^{1}H NMR spectroscopic data (Table 2), the protons of the alkyl substituents in 1H-4-hydroxy-2-oxoquinoline-3-acetic acid dialkylamides (**1e-i**) are magnetically nonequivalent and this is evidently due to specific structural features in these compounds. An X-ray structural investigation (Tables 3-5) carried out in the case of dibutylamide **1g**, confirms this proposal and allows us to show that the dibutylamino group has a planar-trigonal

TABLE 1. Characteristics of 1H-4-Hydroxy-2-oxoquinoline-3-acetic Acid N-Substituted Amides **1a-j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (ethanol)	Yield, %
		C	H	N		
1a*	$C_{19}H_{18}N_2O_3$	70.66 / 70.79	5.74 / 5.63	8.61 / 8.69	244-246	98
1b*[2]	$C_{19}H_{18}N_2O_3$	70.83 / 70.79	5.60 / 5.63	8.77 / 8.69	244-246	96
1c	$C_{19}H_{18}N_2O_3$	70.70 / 70.79	5.69 / 5.63	8.62 / 8.69	240-242	99
1d	$C_{18}H_{16}N_2O_3$	70.01 / 70.12	5.29 / 5.23	9.14 / 9.09	256-258	74
1e	$C_{15}H_{18}N_2O_3$	65.61 / 65.68	6.70 / 6.61	10.14 / 10.21	208-210	87
1f	$C_{17}H_{22}N_2O_3$	67.48 / 67.53	7.40 / 7.33	9.21 / 9.26	198-200	76
1g	$C_{19}H_{26}N_2O_3$	69.15 / 69.06	7.87 / 7.93	8.54 / 8.48	154-156	90
1h	$C_{21}H_{30}N_2O_3$	70.35 / 70.36	8.48 / 8.44	7.76 / 7.81	172-174	89
1i	$C_{25}H_{22}N_2O_3$	75.44 / 75.36	5.50 / 5.57	7.09 / 7.03	202-204	94
1j	$C_{15}H_{16}N_2O_4$	62.41 / 62.49	5.63 / 5.59	9.68 / 9.72	191-193	91

* $[\alpha]^{20}_{578}$ -128.8; $[\alpha]^{20}_{546}$ -150.2 (c = 0.04 g/ml in DMSO).
*[2] $[\alpha]^{20}_{578}$ +128.8; $[\alpha]^{20}_{546}$ +150.2 (c = 0.04 g/ml in DMSO).

TABLE 2. ^{1}H NMR Spectral Characteristics of 1H-4-Hydroxy-2-oxoquinoline-3-acetic Acid N-Substituted Amides **1a-j**, ppm

Com-pound	OH (1H, s)	NH (1H, s)	5-H (1H, d)	7-H (1H, t)	8-H (1H, d)	6-H (1H, t)	CH_2CO (2H, s)	
1a	12.09	11.43	7.84	7.50	7.31 (6H, m, 8-H + Ph)	7.12	3.67	9.04 (1H, d, NH); 4.93 (1H, q, CH); 1.37 (3H, d, Me)
1b	12.09	11.42	7.85	7.48	7.31 (6H, m, 8-H + Ph)	7.14	3.67	9.03 (1H, d, NH); 4.95 (1H, q, CH); 1.36 (3H, d, Me)
1c	12.09	11.40	7.83	7.48	7.30 (6H, m, 8-H + Ph)	7.14	3.67	9.00 (1H, d, NH); 4.94 (1H, q, CH); 1.36 (3H, d, Me)
1d	11.18	10.69	7.85	7.45 (6H, m, 7-H + Ph)	7.32	7.09	3.44	3.23 (3H, s, Me)
1e	11.98	11.39	7.83	7.49	7.27	7.15	3.72	3.53 (2H, q, NCH_2); 3.33 (2H, q, NCH_2); 1.22 (3H, t, Me); 1.03 (3H, t, Me)
If	12.00	11.41	7.86	7.47	7.26	7.15	3.73	4.48 (1H, m, CH); 3.59 (1H, m, CH); 1.26 (6H, d, Me × 2); 1.17 (6H, d, Me × 2)
1g	11.97	11.40	7.84	7.49	7.27	7.15	3.72	3.47 (2H, t, NCH_2); 3.28 (2H, t, NCH_2); 1.37 (8H, m, $(C\underline{H}_2)_2Me$ × 2); 0.95 (3H, t, Me); 0.86 (3H, t, Me)
1h	11.98	11.41	7.84	7.50	7.28	7.14	3.74	3.46 (2H, t, NCH_2); 3.21 (2H, t, NCH_2); 1.69-1.37 (6H, m, $C\underline{H}_2C\underline{H}(Me)_2$ × 2); 0.96 (6H, d, Me × 2); 0.85 (6H, d, Me × 2)
1i	12.01	11.36	7.88	7.50	7.36 (6H, m, 8-H + Ph)	7.18 (6H, m, 6-H + Ph)	3.80	4.73 (2H, s, CH_2); 4.49 (2H, s, CH_2)
1j	11.93	11.37	7.86	7.43	7.29	7.12	3.72	3.80 (2H, s, CH_2); 3.58 (6H, s, $(CH_2)_3$)

TABLE 3. Coordinates for Non-hydrogen Atoms ($\times 10^4$), Hydrogen Atoms ($\times 10^3$), and Equivalent Isotropic Thermal Parameters (Å$\times 10^3$) in the Structure of Dibutylamide **1g**

Atom	*x*	*y*	*z*	U_{eq}
$N_{(1)}$	3853(2)	-1456(1)	3879(1)	49(1)
$C_{(2)}$	3598(2)	-421(2)	3161(1)	44(1)
$O_{(21)}$	4286(1)	761(1)	3599(1)	57(1)
$C_{(3)}$	2514(2)	-745(2)	1920(1)	43(1)
$C_{(4)}$	1799(2)	-2059(2)	1521(1)	44(1)
$O_{(41)}$	789(1)	-2444(1)	370(1)	58(1)
$C_{(5)}$	2058(2)	-3111(2)	2327(1)	44(1)
$C_{(6)}$	1287(2)	-4437(2)	1995(2)	55(1)
$C_{(7)}$	1550(2)	-5379(2)	2824(2)	64(1)
$C_{(8)}$	2620(2)	-5029(2)	4001(2)	67(1)
$C_{(9)}$	3394(2)	-3743(2)	4356(2)	60(1)
$C_{(10)}$	3113(2)	-2768(2)	3531(1)	45(1)
$C_{(11)}$	2118(2)	487(2)	1240(2)	51(1)
$C_{(12)}$	2210(2)	257(2)	-199(2)	50(1)
$O_{(121)}$	1640(1)	-860(1)	-992(1)	61(1)
$N_{(13)}$	2855(2)	1252(2)	-625(1)	55(1)
$C_{(14)}$	3426(2)	2651(2)	199(2)	63(1)
$C_{(15)}$	5054(2)	2688(2)	831(2)	75(1)
$C_{(16)}$	5606(3)	4137(3)	1732(2)	81(1)
$C_{(17)}$	7242(3)	4236(4)	2252(3)	101(1)
$C_{(18)}$	2903(2)	1025(2)	-2037(2)	63(1)
$C_{(19)}$	1567(2)	1577(2)	-2866(2)	59(1)
$C_{(20)}$	1718(3)	1545(3)	-4267(2)	73(1)
$C_{(21)}$	407(3)	2106(3)	-5098(3)	90(1)
$H_{(1)}$	4528(19)	-1219(17)	4703(18)	64(5)
$H_{(6)}$	572(20)	-4635(18)	1210(18)	64(5)
$H_{(7)}$	1010(21)	-6309(21)	2575(19)	80(6)
$H_{(8)}$	2803(20)	-5698(21)	4562(19)	79(6)
$H_{(9)}$	4139(20)	-3498(19)	5169(19)	74(5)
$H_{(41)}$	1028(22)	-1845(23)	-211(21)	94(7)
$H_{(111)}$	1118(20)	720(18)	1266(16)	61(5)
$H_{(112)}$	2737(21)	1279(20)	1805(18)	74(6)
$H_{(141)}$	2807(18)	2938(17)	877(17)	60(5)
$H_{(142)}$	3247(20)	3397(21)	-360(20)	81(6)
$H_{(152)}$	5173(24)	1872(25)	1343(22)	102(7)
$H_{(151)}$	5603(23)	2465(22)	75(23)	99(7)
$H_{(161)}$	5047(24)	4376(23)	2502(23)	100(7)
$H_{(162)}$	5221(26)	4956(26)	1275(23)	109(8)
$H_{(171)}$	7709(30)	4176(28)	1461(29)	134(10)
$H_{(172)}$	7494(28)	3379(29)	2733(26)	124(10)
$H_{(173)}$	7533(30)	5206(34)	2874(29)	135(9)
$H_{(181)}$	3799(21)	1477(18)	-2109(17)	65(5)
$H_{(182)}$	3023(19)	-12(23)	-2402(18)	74(6)
$H_{(191)}$	1360(18)	2560(20)	-2440(17)	62(5)
$H_{(192)}$	644(20)	994(19)	-2875(17)	70(5)
$H_{(201)}$	1928(21)	561(24)	-4662(19)	86(6)
$H_{(202)}$	2633(24)	2116(23)	-4196(20)	92(7)
$H_{(211)}$	274(26)	3073(29)	-4777(24)	106(9)
$H_{(212)}$	-563(31)	1553(29)	-5143(25)	127(10)
$H_{(213)}$	627(29)	1959(27)	-6003(29)	132(9)

configuration and is situated in the same plane as the $C_{(12)}$=$O_{(121)}$ group (torsional angle $O_{(121)}$–$C_{(12)}$–$N_{(13)}$–$C_{(18)}$ 0.4°). The butyl substituents are situated in *trans* conformation. The atoms of the quinolone fragment lie in the same plane as carbon atom $C_{(11)}$. The amide fragment is rotated by -60° relative to the endocyclic $C_{(3)}$–$C_{(4)}$ double bond

TABLE 4. Bond Lengths (Å) in Structure **1g**

Bond	*l*	Bond	*l*
$N_{(1)}$–$C_{(2)}$	1.360(2)	$C_{(9)}$–$C_{(10)}$	1.392(2)
$N_{(1)}$–$C_{(10)}$	1.376(2)	$C_{(11)}$–$C_{(12)}$	1.511(2)
$C_{(2)}$–$O_{(21)}$	1.251(2)	$C_{(12)}$–$O_{(121)}$	1.252(2)
$C_{(2)}$–$C_{(3)}$	1.444(2)	$C_{(12)}$–$N_{(13)}$	1.329(2)
$C_{(3)}$–$C_{(4)}$	1,367(2)	$N_{(13)}$–$C_{(14)}$	1.469(2)
$C_{(3)}$–$C_{(11)}$	1.511(2)	$N_{(13)}$–$C_{(18)}$	1.471(2)
$C_{(4)}$–$O_{(41)}$	1.347(2)	$C_{(14)}$–$C_{(15)}$	1.512(2)
$C_{(4)}$–$C_{(5)}$	1.437(2)	$C_{(15)}$–$C_{(16)}$	1.531(3)
$C_{(5)}$–$C_{(6)}$	1.401(2)	$C_{(16)}$–$C_{(17)}$	1.495(3)
$C_{(5)}$–$C_{(10)}$	1.404(2)	$C_{(18)}$–$C_{(19)}$	1.518(3)
$C_{(6)}$–$C_{(7)}$	1.369(2)	$C_{(19)}$–$C_{(20)}$	1.510(3)
$C_{(7)}$–$C_{(8)}$	1.392(3)	$C_{(20)}$–$C_{(21)}$	1.508(3)
$C_{(8)}$–$C_{(9)}$	1.369(3)		

TABLE 5. Bond Angles (deg.) in Structure **1g**

Angle	ω	Angle	ω
$C_{(2)}$–$N_{(1)}$–$C_{(10)}$	124.59(13)	$N_{(1)}$–$C_{(10)}$–$C_{(9)}$	120.89(14)
$O_{(21)}$–$C_{(2)}$–$N_{(1)}$	119.39(13)	$N_{(1)}$–$C_{(10)}$–$C_{(5)}$	118.86(14)
$O_{(21)}$–$C_{(2)}$–$C_{(3)}$	123.03(13)	$C_{(9)}$–$C_{(10)}$–$C_{(5)}$	120.2(2)
$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	117.58(14)	$C_{(12)}$–$C_{(11)}$–$C_{(3)}$	116.76(14)
$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	119.25(14)	$O_{(121)}$–$C_{(12)}$–$N_{(13)}$	120.4(2)
$C_{(4)}$–$C_{(3)}$–$C_{(11)}$	124.37(13)	$O_{(121)}$–$C_{(12)}$–$C_{(11)}$	119.5(2)
$C_{(2)}$–$C_{(3)}$–$C_{(11)}$	115.92(14)	$N_{(13)}$–$C_{(12)}$–$C_{(11)}$	120.1(2)
$O_{(41)}$–$C_{(4)}$–$C_{(3)}$	122.59(14)	$C_{(12)}$–$N_{(13)}$–$C_{(14)}$	124.29(14)
$O_{(41)}$–$C_{(4)}$–$C_{(5)}$	115.70(13)	$C_{(12)}$–$N_{(13)}$–$C_{(18)}$	119.4(2)
$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	121.69(13)	$C_{(14)}$–$N_{(13)}$–$C_{(18)}$	116.1(2)
$C_{(6)}$–$C_{(5)}$–$C_{(10)}$	118.46(14)	$N_{(13)}$–$C_{(14)}$–$C_{(15)}$	113.3(2)
$C_{(6)}$–$C_{(5)}$–$C_{(4)}$	123.57(14)	$C_{(14)}$–$C_{(15)}$–$C_{(16)}$	112.2(2)
$C_{(10)}$–$C_{(5)}$–$C_{(4)}$	117.94(14)	$C_{(17)}$–$C_{(16)}$–$C_{(15)}$	112.7(2)
$C_{(7)}$–$C_{(6)}$–$C_{(5)}$	121.0(2)	$N_{(13)}$–$C_{(18)}$–$C_{(19)}$	112.8(2)
$C_{(6)}$–$C_{(7)}$–$C_{(8)}$	119.6(2)	$C_{(20)}$–$C_{(19)}$–$C_{(18)}$	112.8(2)
$C_{(9)}$–$C_{(8)}$–$C_{(7)}$	120.9(2)	$C_{(21)}$–$C_{(20)}$–$C_{(19)}$	113.4(2)
$C_{(8)}$–$C_{(9)}$–$C_{(10)}$	119.7(2)		

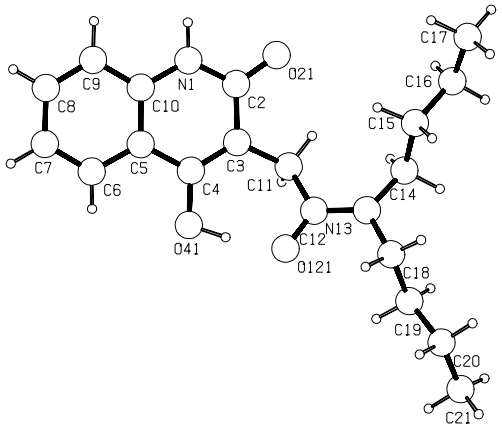

Fig. 1. Overall view of the molecule of compound **1g**.

(torsional angle $C_{(4)}$–$C_{(3)}$–$C_{(11)}$–$C_{(12)}$). Due to the formation of the intramolecular hydrogen bond $O_{(41)}$–$H_{(41)}$–$O_{(121)}$ 1.56 Å (O–H–O angle 171°) the carbonyl group oxygen atom is turned towards the opposite side by 47.4° (torsional angle $C_{(3)}$–$C_{(11)}$–$C_{(12)}$–$O_{(121)}$). In the crystal the molecules form centrosymmetric dimers due to intermolecular hydrogen bonds $N_{(1)}$–$H_{(1)}$–$O_{(21')}$ 1.85 Å (1 - *x*, *y*, 1 - *z*; N–H–O angle 175°).

The action of the synthesized compounds on thyroid gland function was studied by a standard method [3] *via* determination of the concentration of thyroid hormones in animal blood serum. The data obtained showed that 1-phenylethylamides **1a-c** at a dose level of 10 mg/kg demonstrated only weak antithyroid activity but in the *S*(-) conformer (**1a**) this effect is expressed more strongly. In contrast to 1H-4-hydroxy-2-oxoquinoline-3-acetic acid piperidylamide [2], morpholylamide **1j** and N-methylanilide **1d** show thyroid stimulating activity; the increase in concentration of triiodothyronine (T_3) and thyroxine (T_4) being 22-38 and 46-64% respectively. This effect is more marked in diethylamide **1e**, under the influence of which the production of thyroxine by thyroid gland increases to 72% when compared with the control data. Further increase of the hydrocarbon chain in dialkylamide substituents leads to a decrease in the thyroid-stimulating effect and even to the appearance of weak antithyroid activity.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker WP-100SY instrument using DMSO-d_6 as solvent and TMS as internal standard. IR and mass spectra for anhydride **2** were obtained respectively on a Specord M-80 instrument for KBr tablets (concentration 1%) and on a Finnigan MAT Incos 50 quadrupole spectrometer in full scanning mode over the range 33-700 *m/z* with electron impact ionization 70 eV, direct introduction, and a heating rate of about 5° per second. The specific rotation of 1-phenylethylamides **1a,b** was measured on a Polamat A spectropolarimeter. 1H-2-Oxo-4-hydroxyquinoline-3-acetic acid **3** and its methyl ester **5** were prepared according to the method [4].

General Method for Preparing 1H-4-Hydroxy-2-oxoquinoline-3-acetic Acid N-Substituted Amides (1a-j). The corresponding amine (0.011 mol) was added to suspension of 2,3,4,5,-tetrahydrofuro[3,2-*c*]quinoline-2,4-dione **2** (2.01 g, 0.01 mol) in anhydrous pyridine (15 ml) and the whole was refluxed for 0.5-2 h. After cooling, the reaction mixture was treated with water and acidified with HCl to pH 4. The precipitated amide **1** was filtered off, washed with water, and dried.

2,3,4,5-Tetrahydrofuro[3,2-*c*]quinoline-2,4-dione (2). A. Thionyl chloride (0.8 ml, 0.011 mol) was added to suspension of 1H-4-hydroxy-2-oxoquinoline-3-acetic acid **3** (2.19 g, 0.01 mol) in dry carbon tetrachloride (50 ml) and the whole was refluxed for 5 h, after which the solvent was distilled off to a volume of 20 ml. After cooling, the precipitated anhydride **2** was filtered off, washed with dry CCl_4, and dried. Yield 1.85 g (92%); mp > 310°C (an analytically pure sample was obtained by sublimation). Mass spectrum, *m/z*, (I_{rel}, %): 201 (90) $[M]^+$, 172 (100), 119 (22), 92 (27), 58 (23). IR spectrum: 1821 (OCOC), 1667 (CONH), 1606 cm^{-1} (C=C). Found, %: C 65.56; H 3.60; N 6.92. $C_{11}H_7NO_3$. Calculated, %: C 65.67; H 3.51; N 6.96.

B. N,N'-Dicyclohexylcarbodiimide (2.26 g, 0.011 mol) was added to solution of acid **3** (2.19 g, 0.01 mol) in dry dioxane (50 ml) and refluxed for 2 h, then cooled to a temperature of 50°C. The precipitate of anhydride **2** was filtered off, washed on the filter with dioxane, and dried. Yield 1.48 g (74%).

C. 1H-4-Hydroxy-2-oxoquinoline-3-acetic acid methyl ester **5** (2.33 g, 0.01 mol) was held on a metal bath at temperature of 240-250°C for 5-10 min. The reaction mass melted at this time and rapidly solidified. The residue was anhydride **2** which was used in further synthesis without additional purification. Yield 2.0 g (quantitative).

The IR and mass spectra of samples of anhydride **2** obtained by the different methods were identical.

1H-4-Acetoxy-2-oxoquinoline-3-acetic Acid (4). Solution of acid **3** (2.19 g, 0.01 mol) in acetic anhydride (30 ml) was refluxed for 3 h. Excess Ac_2O was evaporated at reduced pressure. Ethyl acetate (20 ml) was added to the residue and it was thoroughly stirred, filtered, washed on the filter with ethyl acetate, and dried. After recrystallization from propan-2-ol, acetoxy derivative **4** was obtained (1.98 g, 76%); mp > 310°C. ^{1}H NMR spectrum: 11.40 (1H, s, NH); 7.88 (1H, d, 5-H); 7.53 (1H, t, 7-H); 7.29 (1H, d, 8-H); 7.17(1H, t, 6-H); 3.60 (2H, s, CH_2); 2.44 (3H, s, Me). Found, %: C 59.85; H 4.18; N 5.47. $C_{13}H_{11}NO_5$. Calculated, %: C 59.77; H 4.24; N 5.36.

X-Ray Investigation. Basic crystallographic data for the structure of dibutylamide **1g**: crystallographic system triclinic; at 20°C a = 9.284(1), b = 9.595(1), c = 10.556(2) Å; α = 101.89(1)°, β = 102.51(1)°, γ = 89.97(3)°; V = 897.3(2) Å^3; d_{calc} = 1.223 g/cm^3; space group $P\bar{1}$; Z = 2. Unit cell parameters and intensities for 3522 independent reflections (R_{int} = 0.014) were measured on a CAD-4 diffractometer (λMoKα, graphite monochromator, $\theta/2\theta$ scanning, $2\theta_{max}$ = 52°). The structure was solved by direct method using the SHELXTL PLUS computer program [5]. The positions of the hydrogen atoms were determined by difference synthesis of electron density. Refinement by F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms (isotropic for hydrogen atoms) was carried out for 2765 reflections to wR_2 = 0.102 (R_1 = 0.0462 for 2367 reflections with $F > 4\sigma(F)$, S = 1.299). The final atomic coordinates are given in Table 3.

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