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4-HYDROXY-2-QUINOLONES. 174.* HYDROCHLORIDES OF [(ALKYLAMINO)ALKYL]AMIDES OF 1-ALLYL-4-HYDROXY-6,7-DIMETHOXY-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACID – A NEW CLASS OF OPIOID RECEPTOR ANTAGONISTS

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Hydrochlorides salts of [(alkylamino)alkyl]amides of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid were synthesized as potential biologically active compounds. Pharmacological testing showed promise for using these compounds to develop new highly efficient opioid receptor antagonists.

Keywords:, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, opioid receptor antagonists amidation.

Opioid receptor antagonists are a separate group of drugs, which have relatively recently appeared on the pharmaceutical market [2]. The best-known members of this class, naloxone and naltrexone, are commonly used in medicine for the elimination of acute intoxication by narcotic analgesics, cessation of the action of such agents, restoration of breathing in neonates after the introduction of related opioid analgesics to women in childbirth, for the diagnosis of addiction to narcotics, and the treatment of addiction to narcotics and alcoholism [3-8]. In addition to their obvious positive properties, both naloxone and naltrexone have a common significant drawback, namely, these compounds both have the chemical structure of semisynthetic morphines and, thus, have many contraindications for use [8, 9]. Furthermore, similar to all morphinanes, these compounds are not highly stable, which leads to difficulties in their preparation and the storage of drug formulations. The high cost of these compounds is also a problem [10]. Improvement in some pharmaceutical and pharmacokinetic properties of naloxone and naltrexone has been achieved by their chemical modification to create prodrugs [11-15]. Nevertheless, in this approach, the biologically active basis is not altered in principle and, thus, many of the problems indicated remain unresolved.

*For Communication 173, see [1].

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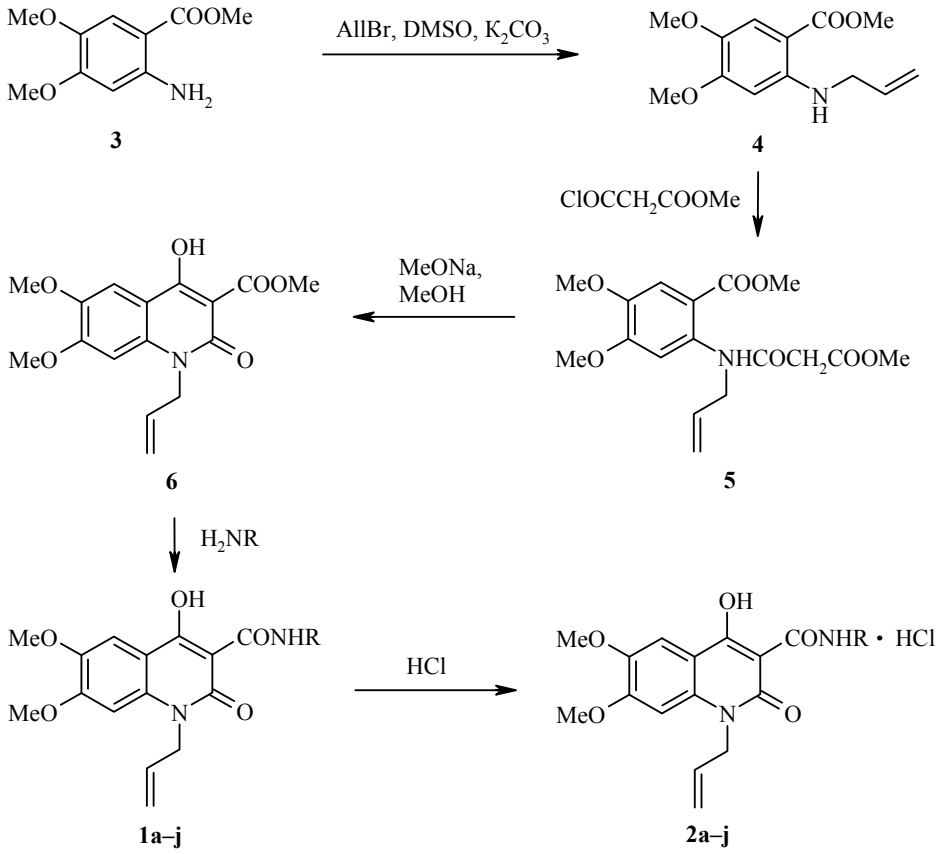
Hence, the search for new, highly efficient opioid receptor antagonists among the more simple and available compounds is an extremely important current concern. This work was initiated with computer screening, which we first carried out for 4-hydroxy-2-quinolones using the program for the Prediction of Activity Spectra for Substances (PASS) [16]. We found that the capacity to block opioid receptors falls in the wide spectrum of biological properties of this class of compounds. While the probability for the manifestation of this type of activity (p_a) proved low, the calculated maximum for this index (0.433) was found for N-R-amides of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid. As noted by the developers of the PASS program, a compound with $p_a < 0.5$ will probably not display activity. However, if in subsequent experiments the pharmacological property predicted with such a low probability nevertheless is found, this implies that a new chemical class of biologically active compounds has been discovered with the given activity. In other words, experimentally established high activity of N-R-amides of 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid would indicate that opioid receptor antagonists with similar structure have not been reported.

In light of these arguments, we obtained a series of [(alkylamino)alkyl]amides of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **1a-j**. The specific selection of N-R-amides of this type is attributed only to the feasibility of their conversion into water-soluble hydrochloride salts **2a-j** and not to some fundamental reason.



1, 2 a R = 2-(dimethylamino)ethyl, **b** R = 2-(ethylamino)ethyl, **c** R = 2-[(2-hydroxyethyl)amino]ethyl, **d** R = 3-(diethylamino)ethyl, **e** R = 3-(dimethylamino)propyl, **f** R = 3-(diethylamino)propyl, **g** R = (1-ethylpyrrolidin-2-yl)methyl, **h** R = 2-morpholin-4-ylethyl, **i** R = 3-morpholin- 4-ylpropyl, **j** R = 3-piperidin-1-ylpropyl

The commercially available methyl ester of 2-amino-4,5-dimethoxybenzoic acid (**3**) was the most rational choice as the starting compound. The N-alkylation of acid **3** by alkyl bromide in the DMSO/K_2CO_3 system proceeds with good yield. Then, N-allylanthranilate **4** was acylated with methyl malonyl chloride, and the resultant anilide **5** undergoes Dieckmann heterocyclization to give the methyl ester of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**6**).

The amidation of ester **6** by alkylaminoalkylamines may be carried out by a standard procedure [17], i.e., by heating equimolar amounts of the reagents in ethanol at reflux over several hours. We should also note a method usually employed in the synthesis of arylamides and hetarylamides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids involving heating the corresponding esters with amines with the same equimolar reagent ratio [17]. Such a modification permits a shortening of the reaction time to several minutes with retention of high yields.

All the synthesized [(alkylamino)alkyl]amides of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **1a-j** and their hydrochlorides **2a-j** are colorless crystalline compounds with sharp melting points (Table 1), which are readily soluble in DMF and DMSO.

^{1}H NMR spectroscopy was used to establish the structure of the final hydrochlorides **2a-j** (Table 2).

The capacity of the alkylaminoalkylamide hydrochlorides **2a-j** to block opioid receptors was studied in white mice with mass 20-30 g by a method involving the elimination of the analgesic effect of narcotic analgesics, in particular, tramadol, a well-known synthetic opioid [8]. The tested animals were separated into groups of six for each dose and compound studied. The initial pain threshold was found for all the animals using a hot plate [18] (Table 3).

Then, tramadol in dose 10 mg/kg was introduced into the animals intramuscularly in the thigh. The predicted analgesic effect was induced after 60 min and confirmed by retesting of the pain threshold. Then, 60 min after tramadol introduction, the animals of the control group were treated with the reference compound naloxone in dose 1 mg/kg in the same manner, while the animals of the other groups were treated with

TABLE 1. Characteristics of Alkylaminoalkylamide Hydrochlorides **2a-j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2a	$C_{19}H_{25}N_3O_5 \cdot HCl$	55.54 / 55.41	6.45 / 6.36	10.12 / 10.20	251-253 (155-157)	96
2b	$C_{19}H_{25}N_3O_5 \cdot HCl$	55.56 / 55.41	6.49 / 6.36	10.11 / 10.20	244-246 (160-162)	92
2c	$C_{19}H_{25}N_3O_6 \cdot HCl$	53.25 / 53.33	6.01 / 6.12	9.74 / 9.82	223-225 (151-153)	83
2d	$C_{21}H_{29}N_3O_5 \cdot HCl$	57.44 / 57.33	7.02 / 6.87	9.64 / 9.55	210-212 (116-118)	92
2e	$C_{20}H_{27}N_3O_5 \cdot HCl$	56.31 / 56.40	6.50 / 6.63	9.98 / 9.87	235-237 (122-124)	90
2f	$C_{22}H_{31}N_3O_5 \cdot HCl$	58.35 / 58.21	7.23 / 7.11	9.37 / 9.26	206-208 (109-111)	88
2g	$C_{22}H_{29}N_3O_5 \cdot HCl$	58.57 / 58.44	6.84 / 6.69	9.15 / 9.29	197-199 (134-136)	94
2h	$C_{21}H_{27}N_3O_6 \cdot HCl$	55.45 / 55.57	6.09 / 6.22	9.32 / 9.26	231-233 (149-151)	97
2i	$C_{22}H_{29}N_3O_6 \cdot HCl$	56.36 / 56.45	6.60 / 6.46	9.13 / 8.98	221-223 (137-139)	91
2j	$C_{23}H_{31}N_3O_5 \cdot HCl$	59.39 / 59.28	7.05 / 6.92	9.14 / 9.02	230-232 (108-110)	84

* The melting points of the corresponding free bases **1a-j** are given in parentheses.

aminoalkylamide hydrochlorides **2a-j** in doses 1 and 10 mg/kg. As expected, naloxone eliminated the analgesic effect of tramadol as indicated by the return of the pain threshold virtually to the initial level following its injection after only 30 min (Table 3).

TABLE 2. ^{1}H NMR Spectra of Compounds **2a-j**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
2a	16.86 (1H, s, 4-OH); 10.43 (1H, t, *J* = 5.8, CONH); 10.12 (1H, br. s, NH^+); 7.39 (1H, s, H-5); 6.93 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.5, NCH_2CH=C<u>H</u>-*cis*); 5.05 (1H, d, *J* = 17.6, NCH_2CH=C<u>H</u>-*trans*); 4.96 (2H, s, NCH_2); 3.90 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.74 (2H, q, *J* = 6.2, CONHC<u>H_2</u>); 3.29 (2H, t, *J* = 6.3, $NHCH_2C$<u>H_2</u>); 2.79 (6H, s, 2C<u>H_3</u>)
2b	16.94 (1H, s, 4-OH); 10.40 (1H, t, *J* = 5.8, CONH); 8.89 (2H, br. s, NH_2^+); 7.38 (1H, s, H-5); 6.92 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.6, NCH_2CH=C<u>H</u>-*cis*); 5.05 (1H, d, *J* = 17.8, NCH_2CH=C<u>H</u>-*trans*); 4.96 (2H, s, NCH_2); 3.90 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.67 (2H, q, *J* = 6.9, CONHC<u>H_2</u>); 3.11 (2H, quint, *J* = 6.3, NHC<u>H_2</u>CH_3); 2.95 (2H, q, *J* = 7.3, $CONHCH_2C$<u>H_2</u>); 1.18 (3H, t, *J* = 7.2, NCH_2C<u>H_3</u>)
2c	17.02 (1H, s, 4-OH); 10.45 (1H, t, *J* = 5.1, CONH); 9.23 (2H, br. s, NH_2^+); 7.41 (1H, s, H-5); 6.94 (1H, s, H-8); 5.91 (1H, m, C<u>H</u>=CH_2); 5.15 (1H, d, *J* = 10.5, NCH_2CH=C<u>H</u>-*cis*); 5.06 (1H, d, *J* = 17.6, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2); 3.89 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 5.20 (1H, br. s, OH); 3.70 (4H, m, CONHC<u>H_2</u> + NC<u>H_2</u>CH_2OH); 3.17 (2H, t, *J* = 6.2, $CONHCH_2C$<u>H_2</u>); 3.02 (2H, t, *J* = 5.3, NCH_2C<u>H_2</u>OH)
2d	16.88 (1H, s, 4-OH); 10.41 (1H, t, *J* = 5.8, CONH); 10.24 (1H, br. s, NH^+); 7.37 (1H, s, H-5); 6.91 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.6, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.8, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2); 3.90 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 3.73 (2H, q, *J* = 6.4, CONHC<u>H_2</u>); 3.25 (2H, t, *J* = 6.5, $NHCH_2C$<u>H_2</u>); 3.15 (4H, q, *J* = 7.2, $N(C$<u>H_2</u>$CH_3)_2$); 1.22 (6H, t, *J* = 7.2, $N(CH_2C$<u>H_3</u>$)_2$)
2e	17.20 (1H, s, 4-OH); 10.39 (1H, t, *J* = 6.1, CONH); 9.98 (1H, br. s, NH^+); 7.39 (1H, s, H-5); 6.93 (1H, s, H-8); 5.93 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.2, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.7, NCH_2CH=C<u>H</u>-*trans*); 4.96 (2H, s, NCH_2); 3.89 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.43 (2H, q, *J* = 6.2, CONHC<u>H_2</u>); 3.06 (2H, t, *J* = 7.3, $NHCH_2CH_2C$<u>H_2</u>); 2.73 (6H, s, $2CH_3$); 1.94 (2H, quint, *J* = 7.1, $NHCH_2C$<u>H_2</u>CH_2)
2f	17.19 (1H, s, 4-OH); 10.40 (1H, t, *J* = 5.8, CONH); 10.07 (1H, br. s, NH^+); 7.38 (1H, s, H-5); 6.91 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.15 (1H, d, *J* = 10.4, NCH_2CH=C<u>H</u>-*cis*); 5.03 (1H, d, *J* = 17.6, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2); 3.90 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 3.42 (2H, q, *J* = 6.1, CONHC<u>H_2</u>); 3.08 (6H, m, $N(CH_2)_3$); 1.95 (2H, quint, *J* = 6.6, $NHCH_2C$<u>H_2</u>CH_2); 1.18 (6H, t, *J* = 7.3, $N(CH_2C$<u>H_3</u>$)_2$)
2g	16.79 (1H, s, 4-OH); 10.53 (2H, m, CONH + NH^+); 7.35 (1H, s, H-5); 6.89 (1H, s, H-8); 5.93 (1H, m, C<u>H</u>=CH_2); 5.15 (1H, d, *J* = 10.5, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 18.0, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2); 3.89 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 3.71-2.94 (7H, m, NHC<u>H_2</u>$CHN(CH_2)_2$); 2.23-1.69 (4H, m, 3'-CH_2 + 4'-CH_2); 1.24 (3H, t, *J* = 6.7, NCH_2C<u>H_3</u>)
2h	16.96 (1H, s, 4-OH); 10.97 (1H, br. s, NH^+); 10.42 (1H, t, *J* = 5.6, CONH); 7.36 (1H, s, H-5); 6.90 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.6, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.3, NCH_2CH=C<u>H</u>-*trans*); 4.94 (2H, s, NCH_2); 3.89 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 3.76 (6H, m, CONHC<u>H_2</u> + $O(CH_2)_2$); 3.07 (6H, m, $N(CH_2)_3$)
2i	17.20 (1H, s, 4-OH); 10.87 (1H, br. s, NH^+); 10.38 (1H, t, *J* = 5.8, CONH); 7.38 (1H, s, H-5); 6.91 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.6, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.4, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2); 3.90 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 4.00-3.67 (4H, m, CH_2OCH_2); 3.43 (2H, q, *J* = 6.0, NHC<u>H_2</u>); 3.35-2.91 (6H, m, $CH_2N(CH_2)_2$); 2.01 (2H, quint, *J* = 7.6, $NHCH_2C$<u>H_2</u>CH_2N)
2j	17.19 (1H, s, 4-OH); 10.37 (1H, t, *J* = 5.8, CONH); 10.14 (1H, br. s, NH^+); 7.37 (1H, s, H-5); 6.91 (1H, s, H-8); 5.92 (1H, m, C<u>H</u>=CH_2); 5.16 (1H, d, *J* = 10.5, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.3, NCH_2CH=C<u>H</u>-*trans*); 4.95 (2H, s, NCH_2); 3.89 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 3.41 (4H, m, CONHC<u>H_2</u>CH_2C<u>H_2</u>); 3.03 (2H, m, 2-CH_2 piperidine); 2.82 (2H, m, 6-CH_2 piperidine); 2.00 (2H, quint, *J* = 7.8, $NHCH_2C$<u>H_2</u>CH_2); 1.72 (6H, m, 3,4,5-CH_2 piperidine)

TABLE 3. Biological Characteristics of Compounds **2a-j**

Compound	Dose, mg/kg	Pain threshold level, sec		
		Initial	60 min after tramadol introduction	30 min after introduction of test compound*
2a	1	14.0 ± 1.05	34.4 ± 4.06	21.4 ± 2.15 (+ 52.9 %)
	10	9.2 ± 0.77	22.6 ± 2.34	17.9 ± 1.37 (+ 94.6 %)
2b	1	8.8 ± 0.63	12.2 ± 1.10	11.3 ± 0.88 (+ 28.4 %)
	10	14.3 ± 1.10	18.5 ± 1.52	10.2 ± 0.81 (– 28.7 %)
2c	1	19.0 ± 1.22	36.0 ± 4.13	34.0 ± 3.56 (+ 78.9 %)
	10	8.6 ± 0.58	12.7 ±1.05	23.8 ± 2.48 (+ 176.7 %)
2d	1	14.0 ± 0.94	22.6 ± 2.77	34.8 ± 3.70 (+ 148.6 %)
	10	9.4 ± 0.60	20.4 ± 2.08	35.9 ± 3.82 (+ 281.9 %)
2e	1	13.8 ± 0.91	25.6 ± 3.03	17.5 ± 1.33 (+ 26.8 %)
	10	9.2 ± 0.61	18.4 ± 1.75	12.0 ± 0.95 (+ 30.4 %)
2f	1	8.5 ± 0.53	16.6 ± 1.50	23.6 ± 2.02 (+ 177.6 %)
	10	10.8 ± 0.92	20.8 ± 1.82	19.2 ± 2.10 (+ 77.7 %)
2g	1	19.6 ± 1.37	34.2 ± 3.30	16.4 ± 1.27 (– 16.3 %)
	10	12.4 ± 0.88	23.6 ± 2.54	10.3 ± 0.75 (– 16.9 %)
2h	1	8.4 ± 0.49	17.2 ± 1.21	15.5 ± 1.22 (+ 84.5 %)
	10	7.6 ± 0.35	35.1 ± 3.75	60.0 ± 8.50 (+ 689.5 %)
2i	1	15.5 ± 1.22	33.6 ± 3.44	12.7 ± 0.91 (– 18.1 %)
	10	17.3 ± 1.38	24.9 ± 2.46	11.2 ± 0.84 (– 35.3 %)
2j	1	11.5 ± 0.96	13.4 ± 1.03	18.1 ± 1.53 (+ 57.4 %)
	10	17.6 ± 1.43	15.7 ± 1.27	30.5 ± 3.44 (+ 73.3 %)
Naloxone	1	18.9 ± 1.40	38.5 ± 3.93	19.5 ± 1.52 (+ 3.2 %)

*The changes of the pain threshold level in % relative to the initial data are given in parentheses.

Considering that the pain threshold in animals receiving only tramadol rises by 104% after 90 min following introduction in comparison with the initial data, naloxone-like action could be established reliably only for a few of our compounds, namely, amides **2b,e,g,i,j**. In this case, 2-(ethylamino)ethyl derivative **2b** in dose 10 mg/kg while (1-ethylpyrrolidin-2-yl)methyl derivative **2g** and 3-morpholin-4-ylpropyl derivative **2i** in dose 1 mg/kg exceed the level of specific action of the naloxone reference. We should note that under the action of these compounds, the pain sensitivity of the tested animals is even somewhat higher than the initial level. The reason for this effect may be blocking of the opioid receptors not only for their classical agonist tramadol but also for their own endorphins and encephalins, which act as internal natural analgesics.

Some of the alkylaminoalkylamide hydrochlorides tested such as **2a** have almost no effect on the pain sensitivity threshold while the remaining compounds, especially (2-morpholin-4-ylethyl)amide **2h** in dose 10 mg/kg, markedly raise the threshold and thereby significantly strengthen the analgesic effect of tramadol. We should note the strong similarity of the structures of (2-morpholin-4-ylethyl)amide **2h** and (3-morpholin-4-ylpropyl)amide **2i**, which differ fundamentally in their biologic activity. Minimal structural differences between agonists and antagonists of opioid receptors have long been the subject of scientific discussion [19].

EXPERIMENTAL

The ^{1}H NMR spectra of the products were taken on a Varian Mercury-VX-200 spectrometer at 200 MHz in DMSO-d_6 with TMS as the internal standard.

Commercial samples of the methyl ester of 2-amino-4,5-dimethoxybenzoic acid (**3**) and methyl malonyl chloride obtained from Fluka were used in these experiments.

Methyl Ester of 1-Allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (6). Anhydrous potassium carbonate (20.7 g, 0.15 mol) and alkyl bromide (9.3 ml, 0.011 mol) were added to a solution of methyl ester of 2-amino-4,5-dimethoxybenzoic acid (**3**) (21.12 g, 0.1 mol) in DMSO (70 ml) and stirred for 5 h at 90°C. After cooling, the reaction mixture was diluted by adding cold water. The N-allyl-substituted ester formed **4** was extracted with four 100-ml portions of dichloromethane. The organic extracts were combined and ~100 ml solvent was then distilled off. Triethylamine (15.4 ml, 0.11 mol) was added to the solution of ester **4** in CH_2Cl_2. Then, methyl malonyl chloride (11.8 ml, 0.11 mol) was added dropwise with cooling and stirring. The solution was left to stand at room temperature for 5 h and then diluted by adding water. The organic layer was separated and dried over anhydrous calcium chloride. The solvent was distilled off, initially at atmospheric pressure and then under reduced pressure. A solution of sodium methylate obtained by adding metallic sodium (3.45 g, 0.15 mol) to absolute methanol (80 ml) was added to residue, the mixture was heated to reflux, and left for 10-12 h at room temperature. The reaction mixture was diluted by adding cold water and acidified by adding a 1:1 solution of concentrated hydrochloric acid and water to pH 4.5-5.0. The precipitate of ester **6** was filtered off, washed with water, and dried to give 24.27 g (76%) **6**; mp 174-176°C (methanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.46 (1H, s, OH); 7.31 (1H, s, H-5); 6.78 (1H, s, H-8); 5.86 (1H, m, C<u>H</u>=CH_2); 5.13 (1H, d, *J* = 10.6, NCH_2CH=C<u>H</u>-*cis*); 5.04 (1H, d, *J* = 17.9, NCH_2CH=C<u>H</u>-*trans*); 4.82 (2H, d, *J* = 4.4, NCH_2); 3.87 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.79 (3H, s, CO_2CH_3). Found, %: C 60.32; H 5.46; N 4.28. $C_{16}H_{17}NO_6$. Calculated, %: C 60.18; H 5.37; N 4.39.

2-[(Dimethylamino)ethyl]amide of 1-Allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (1a). A. 2-(Dimethylamino)ethylamine (1.1 ml, 0.01 mol) was added to a solution of ester **6** (3.19 g, 0.01 mol) in ethanol (15 ml) and heated at reflux for 3 h. The solution was purified with activated charcoal and then maintained for 7-8 h at 0°C. The crystalline precipitate of [(dimethylamino)ethyl]amide **1a** was filtered off, washed with cold ethanol, and dried to give 3.26 g (87%) **1a**.

B. A mixture of ester **6** (3.19 g, 0.01 mol) and 2-(dimethylamino)ethylamine (1.1 ml, 0.1 mol) was maintained in a metal bath at 140°C for 3-5 min, permitting the methanol formed to distill off. The residue was cooled, dissolved in ethanol, and then treated as in procedure A to give 3.41 g (91%) **1a**.

Mixed melting points of samples of [(dimethylamino)ethyl]amide **1a** synthesized by the different methods as well as the derived hydrochlorides proved undepressed.

Hydrochloride of 2-[(Dimethylamino)ethyl]amide of 1-Allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (2a). 2-Propanol saturated with gaseous HCl was added to a solution compound **1a** (3.75 g, 0.01 mol) in 2-propanol (15 ml) to pH 3. Then, dry diethyl ether (10 ml) was added and maintained for 5 h at 0°C. The precipitate of hydrochloride **2a** was filtered off, washed with dry diethyl ether, and dried.

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