

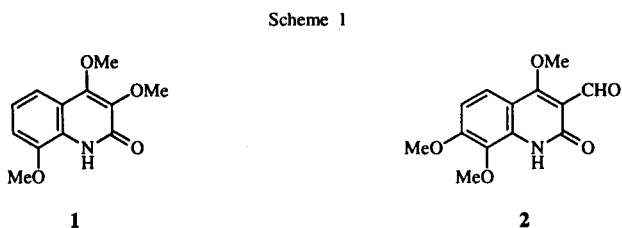
A Convenient Preparation of 4,8-Dimethoxy-3-substituted-2(1H)-quinolones by an Electrophilic Reaction through Base-induced Deprotonation and its Synthetic Application for the Synthesis of New Alkaloids, 3,4,8-Trimethoxy-2(1H)-quinolone and 3-Formyl-4,7,8-trimethoxy-2(1H)-quinolone (Glycocitridine)  
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Some 4,8-dimethoxy-3-substituted-2(1H)-quinolones were prepared by electrophilic reaction of 4,8-dimethoxy-2(1H)-quinolone with electrophiles in the presence of *n*-butyllithium-*N,N,N',N'*-tetramethylethylenediamine in fairly good yields. This present method was successfully applied for the synthesis of two new alkaloids bearing the 4,8-dimethoxy-2(1H)-quinolone skeleton.

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Recently, some new alkaloids which are 4,8-dimethoxy-2(1H)-quinolone derivatives with a functional group at the 3-position have successively been reported and typical examples are 3,4,8-trimethoxy-2(1H)-quinolone **1** [1] from *Eriostemon Gardneri* and 3-formyl-4,7,8-trimethoxy-2(1H)-quinolone **2** [2] (Glycocitridine) from *Glycosmis Citrifolia* (Scheme 1).



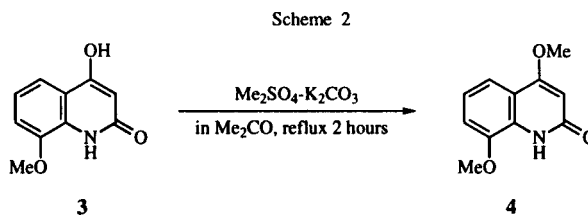
Their structural features are to have a 2(1H)-quinolone skeleton and the functional group at the 3-position. It seems to be difficult synthetically to prepare 2(1H)-quinolone derivatives bearing a functional group at the 3-position by an electrophilic reaction, since the electrophilic reaction has taken place not at the 3-position but mainly at the 6-position in the Friedel-Crafts reaction of 1-methyl-2(1H)-quinolone with benzoyl chloride [3].

Biologically, *Glycosmis Citrifolia* has been used for the treatment of skin diseases in folk medicine [2] thus **2** would be expected to show some pharmacological activity. Moreover, recent investigation using structure-activity relationships indicated to us that a series of 2(1H)-quinolones bearing various acidic moieties at the 3-position has the possibility to become  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainate and *N*-methyl-D-aspartic acid/glycine antagonists which seems to be promising as therapeutic agents for stroke and other ischemic conditions [4]. Accordingly, developing facile methods to prepare a 2(1H)-quinolone with a functional

group at the 3-position is of interest and importance from a synthetic and biological point of view.

We report herein the synthesis of 4,8-dimethoxy-3-substituted-2(1H)-quinolones by an electrophilic reaction through base-induced deprotonation and the synthetic application of this reaction for the synthesis of new alkaloids, **1** and **2**.

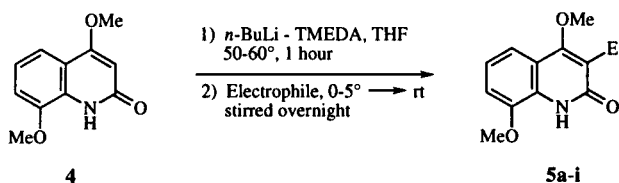
The selective *O*-methylation of 4-hydroxy-8-methoxy-2(1H)-quinolone **3** [5] prepared by reaction of *o*-anisidine with malonic acid in phosphorus oxychloride was investigated using phase transfer catalysis-iodomethane, diazomethane, potassium *t*-butoxide-iodomethane, potassium carbonate-iodomethane, silver(I) oxide-iodomethane, methanol-sulfuric acid, methanol-*p*-toluenesulfonic acid and dimethyl sulfate-potassium carbonate to obtain 4,8-dimethoxy-2(1H)-quinolone **4**. It has been found that **4** is obtained by using dimethyl sulfate-potassium carbonate in acetone and refluxing for 2 hours provides the best yield (74%) (Scheme 2).



The synthesis of 3-substituted-2(1H)-quinolones was recently reported *via* regioselective lithiation of 2(1H)-quinolone [6]. Modifying the method to find the optimal reaction conditions to the synthesis of 4,8-dimethoxy-3-substituted-2(1H)-quinolones, we carried out the electrophilic reaction of **4** with the various types of electrophiles (2 equivalents) in the presence of *n*-butyllithium (4 equivalents)-*N,N,N',N'*-tetramethylethylenediamine

(3.4 equivalents) in tetrahydrofuran to afford the corresponding 3-substituted derivatives in 10-93% yields as shown in Table 1.

Table 1



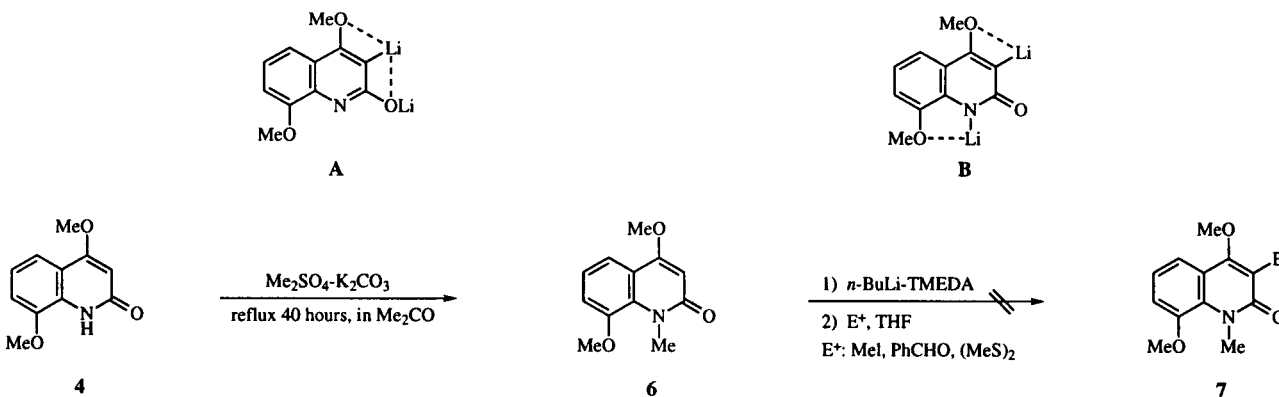
Compound No.	Electrophile	E	Yield (%)
5a	HCONMe <sub>2</sub>	CHO	60
5b	(MeS) <sub>2</sub>	SMe	93
5c	PhCHO	CH(OH)Ph	62
5d	Me <sub>3</sub> SiCl	SiMe <sub>3</sub>	77
5e	MeI	Me	77
5f	Ph <sub>2</sub> CO	C(OH)Ph <sub>2</sub>	44
5g	I <sub>2</sub>	I	27
5h	CH <sub>2</sub> =CHCH <sub>2</sub> Br	CH <sub>2</sub> =CHCH <sub>2</sub>	10
5i	B(OMe) <sub>3</sub>	B(OH) <sub>2</sub>	90

It is possible to postulate that the reason why the present electrophilic reaction takes place selectively at the 3-position is the presence of two lithiated intermediates A and B which are stabilized by the interaction between the lithium atom and the methoxy group or the phenoxide anion (Scheme 3).

nation in intermediate B and the regioselectivity may be controlled only by virtue of the interaction between the C<sub>4</sub>-methoxy group and the lithium atom at 3-position. Actually it was revealed in the electrophilic reaction of 8-methoxy-2(1H)-quinolone with an electrophile in the presence of *n*-butyllithium-*N,N,N,N*-tetramethylethylenediamine at -78° that tandem nucleophile-electrophile addition to the C<sub>4</sub>=C<sub>3</sub> bond took place in place of the expected electrophilic reaction at the C<sub>3</sub>-position [10]. In order to shed light on the contribution of the possible intermediate B towards the present electrophilic reaction, 1-methyl-4,8-dimethoxy-2(1H)-quinolone 6 which is obtainable from 4 in 72% yield using dimethyl sulfate-potassium carbonate was subjected to the aforementioned electrophilic reaction to give only an unknown aliphatic product (mp 219°) without the desired 3-substituted product 7. This fact indicates that the participation of the phenoxide anion in the stabilization of lithiation might be inevitable besides the directed *ortho* metalation effect by the C<sub>4</sub>-methoxy group to give rise to regioselectivity at the C<sub>3</sub>-position.

The present electrophilic reaction was used for the synthesis of 1 and 2. Oxidation of 4,8-dimethoxy-3-boronic acid 5i in Table 1 using 32% peracetic acid gave 3-hydroxy-4,8-dimethoxy-2(1H)-quinolone 8 in 41% yield. The selective *O*-methylation of 8 was achieved using dimethyl sulfate-potassium carbonate to afford the desired alkaloid 1 in 21% yield; the spectral data coinciding

Scheme 3

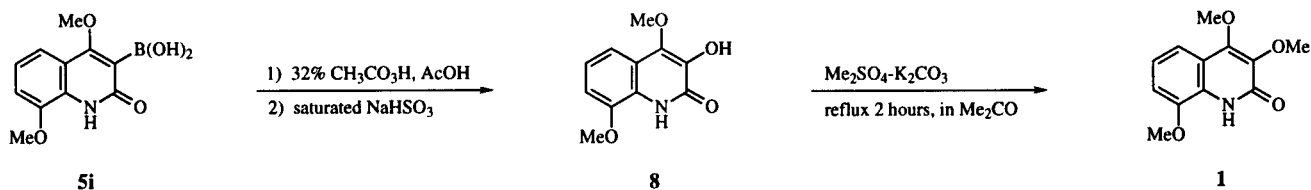


It is conceivable in intermediate A that a phenolic OLi is a directing metalation group [7] and such a dianion associated with two lithium cations can be considered as an ion triplet [8] which strongly contributes towards the stability of A due to Coulombic interaction as well as the stabilization by the interaction between the lithium atom and the methoxy group [9]. On the other hand, the C<sub>8</sub>-methoxy group stabilizes the *N*-lithium salt by coordi-

completely with the data reported in the original paper [1] (Scheme 4).

2,3-Dimethoxyaniline 9 [11] obtained *via* 2-methoxy-6-nitrophenol [12] and 2,3-dimethoxynitrobenzene [11a] starting from 2-methoxyphenol (guaiacol) was cyclized by heating with malonic acid in phosphorus oxychloride into 4-hydroxy-7,8-dimethoxy-2(1H)-quinolone 10 in 62% yield which is easily methylated using dimethyl sul-

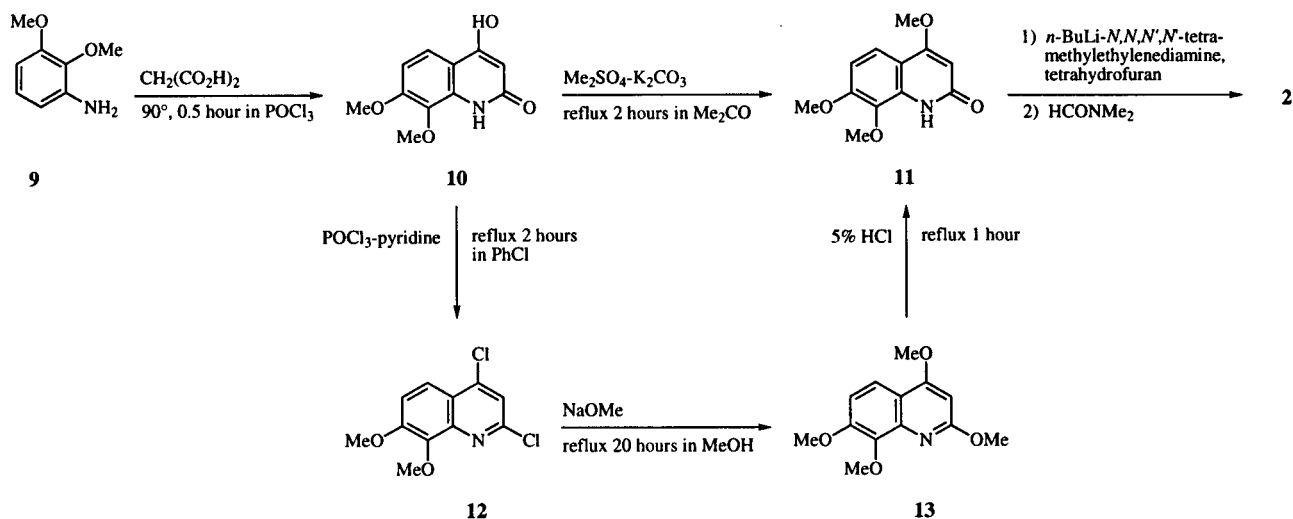
Scheme 4



fate-potassium carbonate into 4,7,8-trimethoxy-2(1*H*)-quinolone **11** in 73% yield. Compound **11** could be also obtained *via* 2,4-dichloro-7,8-dimethoxyquinoline **12** (78%) and 2,4,7,8-tetramethoxyquinoline **13** (78%) from compound **10** as shown in Scheme 5 [13].

are deuterium oxide exchangeable, respectively. The spectral data of the original compound is insufficient with the lack of <sup>13</sup>C- and 2D-nmr spectra. Thus we suppose that a reinvestigation of the structure determination of the original compound in greater detail would be necessary.

Scheme 5



Compound **11** was treated with *N,N*-dimethylformamide as the electrophile under the same reaction conditions as mentioned above to give the desired product **2** in 54% yield. The structure of the thus obtained **2** was unambiguously determined by its reactivity and the spectral data including 1D-, 2D-nmr, mass, and ir spectra. However it must be disclosed that some of the spectral data are different from those reported in the original paper [2] as well as the melting point. The melting point of the synthetic compound is 239-240° dec, and the original one is 174-175° and the appreciable difference is observed in the fragmentation patterns of the ms (EI) and in the ir spectra. Both <sup>1</sup>H nmr spectra in deuteriochloroform resemble each other so much except for a small difference of the NH proton chemical shift between the synthetic compound ( $\delta$  9.12) and the original one ( $\delta$  8.95) which

## EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometers and spectrometers: ir spectra, JASCO IR-810; <sup>1</sup>H nmr spectra, JEOL GX-400 (400 MHz) and JEOL A-500 (500 MHz); <sup>13</sup>C nmr spectra, JEOL GX-400 (100 MHz) and JEOL A-500 (125 MHz); mass spectra, JEOL JMS-DX300 for EI-ms and JMS-HX110 for FAB-ms. The HH-COSY, CH-COSY, and DEPT experiments were also used for the assignments of the structures. The chemical shifts are given on the  $\delta$  scale. Elemental analyses were performed on a Heraeus CHN-O-RAPID instrument. Medium pressure liquid chromatography (mplc) was carried out with a Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40  $\mu$ m, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).

4,8-Dimethoxy-2(1*H*)-quinolone (4).

Dimethyl sulfate (0.54 ml, 5.7 mmoles) was added dropwise to a solution of 4-hydroxy-8-methoxy-2(1*H*)-quinolone **3** (0.91 g, 4.75 mmoles) and potassium carbonate (1.31 g, 9.5 mmoles) in acetone (150 ml) and the resulting solution was refluxed for 2 hours. After the reaction the precipitate was filtered and washed with sufficient water and then recrystallized from ethyl acetate to give 0.36 g of **4** as pale yellow prisms. The filtrate was subjected to column chromatography on silica gel using chloroform as the eluent to give another 0.36 g of **4**. The total yield was 0.72 g (74%). The mp and ir spectrum of this compound coincided with those of the authentic sample [5].

General Procedure for Electrophilic Reaction of 4,8-Dimethoxy-2(1*H*)-quinolones with Electrophiles in the Presence of *n*-Butyllithium-*N,N,N',N'*-tetramethylethylenediamine.

To a solution of 4,8-dimethoxy-2(1*H*)-quinolones (2.13 mmoles), *N,N,N',N'*-tetramethylethylenediamine (1.25 ml, 8.31 mmoles) and tetrahydrofuran (20 ml) was added dropwise 1.64*M n*-butyllithium (5.24 ml, 8.52 mmoles) at -70° under nitrogen with stirring and the solution was allowed to reach room temperature and then further stirred at room temperature for 2 hours. After the resulting solution was heated at 50-60° for 1 hour, it was cooled to 0-5° with ice and electrophile (4.26 mmoles) was added dropwise to the solution. The reaction mixture was stirred at room temperature overnight and then was quenched with a little amount of ice and 2*N*-hydrochloric acid (13 ml) under cooling. The resulting solution was extracted with dichloromethane and after removal of the solvent the residue was worked up in the manner as shown below.

3-Formyl-4,8-dimethoxy-2(1*H*)-quinolone (5a).

The residue was purified by mplc (hexane:ethyl acetate = 2:1) to give 0.3 g (60%) of **5a**. This compound was recrystallized from ethyl acetate to give yellow prisms, mp 181°; ir (potassium bromide): 3150, 1651, 1542, 1488, 1351, 1104 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 3.99 (3H, s, OMe-8), 4.16 (3H, s, OMe-4), 7.06 (1H, d, J = 8.1 Hz, H-7), 7.15 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.58 (1H, d, J = 8.1 Hz, H-5), 9.29 (1H, s, NH), 10.49 (1H, s, CHO); <sup>13</sup>C nmr (deuteriochloroform): δ 56.2 (q, OMe-8), 64.6 (q, OMe-4), 112.8 (d, C-7), 117.0 (d, C-5), 117.5 (s, Ar), 122.4 (d, C-6), 130.2 (s, Ar), 145.5 (s, Ar), 163.6 (s, Ar), 169.3 (s, C=O), 190.2 (s, CHO); ms: m/z (relative intensity) 277 (M<sup>+</sup>, 20), 262 (87), 261 (100), 247 (21), 246 (23), 131 (10), 89 (29), 59 (11).

*Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.74; H, 4.68; N, 6.07.

4,8-Dimethoxy-3-methylthio-2(1*H*)-quinolone (5b).

The residue was purified by mplc (hexane:ethyl acetate = 2:1) to give 0.50 g (93%) of **5b**. This compound was recrystallized from hexane-diethyl ether to give colorless scales, mp 161-162°; ir (potassium bromide): 3400-2800, 1625, 1555, 1360, 1270, 1080, 730 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 2.50 (3H, s, SMe), 3.97 (3H, s, OMe-8), 4.13 (3H, s, OMe-4), 6.97 (1H, d, J = 8.1 Hz, H-7), 7.14 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.41 (1H, d, J = 8.1 Hz, H-5), 9.17 (1H, br s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 16.9 (q, SMe), 56.1 (q, OMe-8), 61.3 (q, OMe-4), 110.4 (d, C-7), 115.1 (d, C-5), 117.8 (s, Ar), 118.2 (s, Ar), 122.0 (d, C-6), 127.8 (s, Ar), 145.6 (s, Ar), 162.1 (s, Ar), 166.0 (s, C=O); ms: m/z (relative intensity) 251 (M<sup>+</sup>, 100), 236 (59), 218 (74), 204 (19), 175 (21), 118 (9).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>S: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.39; H, 5.34; N, 5.66.

3-( $\alpha$ -Hydroxybenzyl)-4,8-dimethoxy-2(1*H*)-quinolone (5c).

The residue was purified by mplc (hexane:ethyl acetate = 2:1) to give 0.41 g (62%) of **5c**. This compound was recrystallized from diethyl ether-acetone to give colorless prisms, mp 212°; ir (potassium bromide): 3600-2600, 1630, 1489, 1384, 1273, 1075, 983, 708, 655 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 3.94 (3H, s, OMe-8), 3.96 (3H, s, OMe-4), 6.11-6.20 (2H, m, -CH-OH), 6.98 (1H, d, J = 8.3 Hz, H-7), 7.16-7.22 (2H, m, H-6 and ArH), 7.25-7.31 (2H, m, ArH), 7.39 (1H, d, J = 8.3 Hz, H-5), 7.52-7.55 (2H, m, ArH), 9.99 (1H, s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 56.1 (q, OMe-8), 62.4 (q, OMe-4), 69.7 (d, -CH-OH), 110.4 (d, C-7), 115.2 (d, C-5), 117.3 (s, Ar), 122.5 (d, Ar), 123.2 (s, Ar), 126.0 (d, Ar), 127.1 (d, Ar), 128.2 (d, Ar), 128.3 (s, Ar), 143.7 (s, Ar), 146.3 (s, Ar), 161.9 (s, Ar), 164.2 (s, C=O); ms: m/z (relative intensity) 311 (M<sup>+</sup>, 30), 296 (100), 278 (13), 234 (20), 218 (70), 150 (12), 77 (17).

*Anal.* Calcd. for C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.43; H, 5.50; N, 4.63.

4,8-Dimethoxy-3-trimethylsilyl-2(1*H*)-quinolone (5d).

This reaction was carried out as described in General Procedure but using chlorotrimethylsilane (4 equivalents) as electrophile instead of 2 equivalents. The residue was purified by mplc (hexane:ethyl acetate = 2:1) to give 0.45 g (77%) of **5d**. This compound was recrystallized from hexane to give colorless prisms, mp 167-168°; ir (potassium bromide): 3200-2800, 1623, 1478, 1343, 1265, 1072, 849 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 0.39 (9H, s, SiMe<sub>3</sub>), 3.88 (3H, s, OMe-4), 3.95 (3H, s, OMe-8), 6.94 (1H, d, J = 8.1 Hz, H-7), 7.09 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.32 (1H, d, J = 8.1 Hz, H-5), 8.84 (1H, br s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 0.3 (q, SiMe<sub>3</sub>), 56.0 (q, OMe-8), 63.1 (q, OMe-4), 110.4 (d, C-7), 115.2 (d, C-5), 117.3 (s, Ar), 121.2 (d, C-6), 121.5 (s, Ar), 130.2 (s, Ar), 145.7 (s, Ar), 166.3 (s, Ar), 171.8 (s, C=O); ms: m/z (relative intensity) 277 (M<sup>+</sup>, 20), 262 (87), 261 (100), 247 (21), 246 (23), 131 (10), 89 (29), 59 (11).

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>NO<sub>3</sub>Si: C, 60.62; H, 6.90; N, 5.05. Found: C, 60.53; H, 6.67; N, 5.27.

4,8-Dimethoxy-3-methyl-2(1*H*)-quinolone (5e).

The residue was purified by mplc (hexane:ethyl acetate = 2:1) to give 0.36 g (77%) of **5e**. This compound was recrystallized from hexane-diethyl ether to give colorless prisms, mp 147-148°; ir (potassium bromide): 3200-2800, 1641, 1492, 1375, 1356, 1273, 1078, 754 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 2.20 (3H, s, Me), 3.92 (3H, s, OMe-4), 3.96 (3H, s, OMe-8), 6.94 (1H, d, J = 8.1 Hz, H-7), 7.13 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.36 (1H, d, J = 8.1 Hz, H-5), 9.13 (1H, br s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 9.9 (q, Me), 56.0 (q, OMe-8), 61.0 (q, OMe-4), 109.5 (d, C-7), 114.6 (d, C-5), 117.7 (s, Ar), 119.6 (s, Ar), 121.8 (d, C-6), 127.2 (s, Ar), 145.6 (s, Ar), 162.0 (s, Ar), 164.0 (s, C=O); ms: m/z (relative intensity) 219 (M<sup>+</sup>, 100), 218 (33), 204 (93), 190 (19), 189 (31).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 5.98; N, 6.39.

3-( $\alpha$ -Hydroxy- $\alpha$ -phenylbenzyl)-4,8-dimethoxy-2(1*H*)-quinolone (5f).

After the reaction the insoluble substances from both dichloromethane and water was filtered and the crude product was recrystallized from methanol to give 0.32 g (39%) of **5f** as color-

less prisms, mp 300-301° dec. The residue from dichloromethane fraction was purified by mpc (hexane:ethyl acetate = 2:1) to give another 41 mg (5%) of **5f**. The total yield was 0.36 g (44%); ir (potassium bromide): 3168, 1628, 1612, 1486, 1358, 1270, 1069, 696 cm<sup>-1</sup>; <sup>1</sup>H nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 2.93 (3H, s, OMe-4), 3.92 (3H, s, OMe-8), 7.20-7.32 (13H, m, ArH), 8.50 (1H, s, OH), 11.37 (1H, s, NH); <sup>13</sup>C nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 56.2 (q, OMe-8), 60.8 (q, OMe-4), 80.2 (s, COH), 111.5 (d, C-7), 115.4 (d, C-5), 116.7 (s, Ar), 122.4 (d, C-6), 125.2 (s, Ar), 126.6 (d, Ar), 127.3 (d, Ar), 128.0 (s, Ar), 146.3 (s, Ar), 146.9 (s, Ar), 161.6 (s, Ar), 165.0 (s, C=O); ms: m/z (relative intensity) 387 (M<sup>+</sup>, 54), 372 (100), 354 (43), 338 (14), 310 (21), 294 (23), 278 (21), 232 (12), 105 (17).

*Anal.* Calcd. for C<sub>24</sub>H<sub>21</sub>NO<sub>4</sub>: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.30; H, 5.22; N, 3.65.

### 3-Iodo-4,8-dimethoxy-2(1*H*)-quinolone (**5g**).

The residue was purified by mpc (hexane:ethyl acetate = 2:1) to give 0.19 g (27%) of **5g**. This compound was recrystallized from hexane-ethyl acetate to give colorless scales, mp 205-206°; ir (potassium bromide): 3200-2800, 1658, 1557, 1351, 1274, 1078, 972, 748 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 3.98 (3H, s, OMe-8), 4.04 (3H, s, OMe-4), 7.02 (1H, d, J = 8.1 Hz, H-7), 7.16 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.39 (1H, d, J = 8.1 Hz, H-5), 9.20 (1H, br s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 56.2 (q, OMe-8), 61.3 (q, OMe-4), 87.9 (s, C-3), 110.9 (d, C-7), 114.9 (d, C-5), 117.0 (s, Ar), 122.4 (d, C-6) 128.7 (s, Ar), 145.9 (s, Ar), 160.5 (s, Ar), 167.9 (s, C=O); ms: m/z (relative intensity) 331 (M<sup>+</sup>, 100), 330 (27), 316 (18), 302 (15), 148 (9).

*Anal.* Calcd. for C<sub>11</sub>H<sub>10</sub>NO<sub>3</sub>I: C, 39.90; H, 3.04; N, 4.23. Found: C, 39.87; H, 2.97; N, 4.29.

### 3-Allyl-4,8-dimethoxy-2(1*H*)-quinolone (**5h**).

The residue was purified by mpc (hexane:ethyl acetate = 2:1) to give 0.05 g (10%) of **5h**. This compound was recrystallized from hexane to give colorless powder, mp 112-113°; ir (potassium bromide): 3004, 1651, 1609, 1493, 1377, 1274, 1073, 731 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 3.45-3.47 (2H, m, CH<sub>2</sub>), 3.95 (3H, s, OMe-4), 3.97 (3H, s, OMe-8), 5.03-5.15 (2H, m, =CH<sub>2</sub>), 6.01-6.11 (1H, m, -CH=), 6.95 (1H, d, J = 8.1 Hz, H-7), 7.14 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.35 (1H, d, J = 8.1 Hz, H-5), 9.09 (1H, br s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 28.7 (t, CH<sub>2</sub>), 56.0 (q, OMe-8), 61.9 (q, OMe-4), 109.8 (d, C-7), 114.9 (d, C-5), 115.4 (t, =CH<sub>2</sub>), 117.6 (s, Ar), 121.8 (d, C-6), 121.8 (s, Ar), 135.6 (d, -CH=), 145.7 (s, Ar), 162.4 (s, Ar), 163.3 (s, C=O); ms: m/z (relative intensity) 246 (M<sup>+</sup>+1, 46), 245 (M<sup>+</sup>, 16), 230 (100), 215 (43).

*Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>•0.3H<sub>2</sub>O: C, 66.71; H, 5.78; N, 5.81. Found: C, 67.08; H, 6.27; N, 5.59.

### 4,8-Dimethoxy-2(1*H*)-quinolone-3-boronic Acid (**5i**).

When the resulting solution was extracted with dichloromethane, the precipitate appeared and was filtered. The precipitate was recrystallized from ethyl acetate-methanol to give 0.48 g (90%) of **5i** as colorless powder, mp 241-242°; ir (potassium bromide): 3168, 1633, 1604, 1489, 1401, 1087 cm<sup>-1</sup>; <sup>1</sup>H nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 3.88 (3H, s, OMe-8), 4.00 (3H, s, OMe-4), 7.08-7.11 (2H, m, H-6 and H-7), 7.37 (1H, dd, J = 7.6 and 1.7 Hz, H-5), 8.23 (2H, s, B(OH)<sub>2</sub>), 10.24 (1H, s, NH); <sup>13</sup>C nmr (dimethyl sulfoxide-d<sub>6</sub>): δ 56.0 (q, OMe-8), 57.1 (q, OMe-4), 110.9 (d, C-6), 114.4 (d, C-5), 116.1 (s, Ar), 121.0 (d,

C-7), 128.5 (s, Ar), 145.4 (s, Ar), 163.5 (s, Ar), 166.0 (s, C=O); ms: m/z (relative intensity) 219 (M<sup>+</sup>-30, 18), 205 (100), 204 (86), 190 (18), 176 (31).

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>NO<sub>5</sub>B: C, 53.05; H, 4.86; N, 5.62. Found: C, 53.04; H, 4.74; N, 5.57.

### 4,8-Dimethoxy-1-methyl-2(1*H*)-quinolone (**6**).

A mixture of 4,8-dimethoxy-2(1*H*)-quinolone **4** (0.44 g, 2.15 mmoles), dimethyl sulfate (0.25 ml, 2.58 mmoles) and potassium carbonate (2.97 g, 21.5 mmoles) in acetone (200 ml) was refluxed for 20 hours under stirring and then the resulting solution was filtered. After evaporation of the solvent, the residue from the filtrate was purified by mpc to give 2,4,8-trimethoxyquinoline (0.07 g, 14%) with the mixed solvent of hexane-ethyl acetate (10:1) as eluent and 0.34 g (72%) of **6** with ethyl acetate as eluent. This compound was recrystallized from hexane-diethyl ether to give colorless prisms, mp 143-144°; ir (potassium bromide): 2950, 1628, 1586, 1469, 1390, 1268, 1230, 1073, 820, 738, 658 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 3.89 (3H, s, OMe-4), 3.90 (3H, s, NMe), 3.92 (3H, s, OMe-8), 6.04 (1H, s, H-3), 7.07 (1H, dd, J = 8.1 and 1.5 Hz, H-7), 7.13 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.59 (1H, dd, J = 8.1 and 1.5 Hz, H-5); <sup>13</sup>C nmr (deuteriochloroform): δ 34.8 (q, NMe), 55.7 (q, OMe-8), 56.6 (q, OMe-4), 96.7 (d, C-3), 114.5 (d, C-7), 115.7 (d, C-5), 118.7 (s, Ar), 122.2 (d, C-6), 131.5 (s, Ar), 148.6 (s, Ar), 162.3 (s, Ar), 164.9 (s, C=O); ms: m/z (relative intensity) 219 (M<sup>+</sup>, 100), 204 (98), 189 (30), 174 (51).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.00; H, 6.24; N, 6.49.

### 3-Hydroxy-4,8-dimethoxy-2(1*H*)-quinolone (**8**).

Peracetic acid (32%, 0.89 ml, 4.23 mmoles) was added dropwise to a solution of 4,8-dimethoxy-2(1*H*)-quinolone-3-boronic acid **5i** (0.5 g, 2.01 mmoles) in acetic acid (10 ml) with ice cooling and then the resulting solution was stirred at room temperature for 2 hours followed by the addition of saturated sodium hydrogen sulfite aqueous solution (2 ml). After the solvent was evaporated, the residue was extracted with chloroform and the insoluble substance was filtered off. The filtrate was purified by mpc (hexane-ethyl acetate = 3:1) to give 0.18 g (41%) of **8**. This compound was recrystallized from hexane-diethyl ether to give colorless prisms, mp 188°; ir (potassium bromide): 3400-3000, 1633, 1613, 1584, 1491, 1400, 1271, 1247, 1088, 976, 786 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 3.96 (3H, s, OMe-8), 4.24 (3H, s, OMe-4), 6.86 (1H, br s, OH), 6.88 (1H, d, J = 8.1 Hz, H-7), 7.16 (1H, dd, J = 8.1 and 8.1 Hz, H-6), 7.45 (1H, d, J = 8.1 Hz, H-5), 9.46 (1H, br s, NH); <sup>13</sup>C nmr (deuteriochloroform): δ 56.0 (q, OMe-8), 60.1 (q, OMe-4), 108.0 (d, C-7), 114.4 (d, C-5), 119.1 (s, Ar), 121.8 (s, Ar), 122.6 (d, C-6), 132.2 (s, Ar), 142.9 (s, Ar), 145.7 (s, Ar), 160.1 (s, C=O); ms: (FAB) m/z 222 (MH<sup>+</sup>).

*Anal.* Calcd. for C<sub>11</sub>H<sub>11</sub>NO<sub>4</sub>: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.59; H, 4.86; N, 6.47.

### 3,4,8-Trimethoxy-2(1*H*)-quinolone (**1**).

A mixture of 3-hydroxy-4,8-dimethoxy-2(1*H*)-quinolone **8** (0.44 g, 1.99 mmoles), potassium carbonate (0.55 g, 3.98 mmoles), and dimethyl sulfate (0.23 ml, 2.39 mmoles) in acetone (30 ml) was refluxed for 7 hours and then filtered off to remove insoluble substances. The filtrate was purified by mpc (hexane:ethyl acetate = 1:1) to give 0.1 g (21%) of **1**. The crude

product was recrystallized from diethyl ether to give colorless prisms, mp 143-144°; ir (potassium bromide): 3166, 3014, 1640, 1578, 1492, 1367, 1243, 1200, 1133, 1085, 1024, 732, 704  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  3.95 (3H, s, OMe-8), 3.97 (3H, s, OMe-3), 4.22 (3H, s, OMe-4), 6.92 (1H, dd,  $J = 8.1$  and  $1.1$  Hz, H-7), 7.12 (1H, dd,  $J = 8.1$  and  $8.1$  Hz, H-6), 7.43 (1H, dd,  $J = 8.2$  and  $1.2$  Hz, H-5), 8.99 (1H, br s, NH);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  56.0 (q, OMe-8), 60.6 (q, OMe-3), 60.8 (q, OMe-4), 109.2 (d, C-7), 115.0 (d, C-5), 118.1 (s, Ar), 122.0 (d, C-6), 124.8 (s, Ar), 136.1 (s, Ar), 145.3 (s, Ar), 153.3 (s, Ar), 160.6 (s, C=O); ms:  $m/z$  (relative intensity) 235 ( $\text{M}^+$ , 25), 220 (33), 192 (9), 175 (4), 149 (6), 121 (5), 85 (65), 83 (100), 47 (23).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}_4$ : C, 61.27; H, 5.57; N, 5.95. Found: C, 61.14; H, 5.37; N, 6.07.

#### 4-Hydroxy-7,8-dimethoxy-2(1H)-quinolone (10).

2,3-Dimethoxyaniline **9** (5 g, 32.7 mmoles) was added dropwise to a solution of malonic acid (5.1 g, 49.1 mmoles) and phosphorus oxychloride (30 ml) with stirring under  $10^\circ$  and the resulting solution was gradually heated to  $90^\circ$ . At  $85^\circ$  reflux started spontaneously and after subsiding, the black solution was further heated at  $90^\circ$  for 0.5 hour and then stirred at room temperature overnight. The reaction mixture was poured onto ice and the insoluble substance was filtered off. The crude product was recrystallized from ethyl acetate to give 4.45 g (62%) of **10** as pale yellow prisms, mp 251-255°; ir (potassium bromide): 3600-2200, 1659, 1655, 1651, 1645, 1628, 1596, 1591, 1577, 1489, 1374, 1334, 1285, 1098, 1032, 967, 868, 800  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  3.80 (3H, s, OMe-7), 3.89 (3H, s, OMe-8), 5.64 (1H, s, H-3), 6.94 (1H, d,  $J = 8.8$  Hz, H-6), 7.52 (1H, d,  $J = 8.8$  Hz, H-5), 10.22 (1H, s, NH), 11.22 (1H, br s, OH);  $^{13}\text{C}$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  56.0 (q, OMe-8), 60.3 (q, OMe-7), 96.3 (d, C-3), 107.0 (d, C-6), 109.9 (s, Ar), 118.1 (d, C-5), 133.2 (s, Ar), 133.6 (s, Ar), 153.1 (s, Ar), 162.4 (s, Ar), 163.3 (s, C=O); ms: (FAB)  $m/z$  222 ( $\text{MH}^+$ ).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{11}\text{NO}_4$ : C, 59.73; H, 5.01; N, 6.33. Found: C, 59.92; H, 4.91; N, 6.62.

#### 4,7,8-Trimethoxy-2(1H)-quinolone (11).

This preparation was carried out as in the case of 4,8-dimethoxy-2(1H)-quinolone **4** except using 4-hydroxy-7,8-dimethoxy-2(1H)-quinolone **10** (1.05 g, 4.75 mmoles) in place of 4-hydroxy-8-methoxy-2(1H)-quinolone **3** (0.91 g, 4.75 mmoles). After the insoluble materials were filtered, the filtrate was chromatographed by mpls with a mixed solvent of hexane-ethyl acetate (1:1) to give 0.82 g (73%) of **11**. This compound was recrystallized from ethyl acetate to give colorless prisms, mp 180-181°; ir (potassium bromide): 3300-2800, 1657, 1630, 1398, 1282, 1222, 1103, 1059, 992, 801  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  3.94 (3H, s, OMe-7), 3.94 (3H, s, OMe-8), 3.95 (3H, s, OMe-4), 5.81 (1H, s, H-3), 6.81 (1H, d,  $J = 8.8$  Hz, H-6), 7.57 (1H, d,  $J = 8.8$  Hz, H-5), 8.73 (1H, br s, NH);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  55.9 (q, OMe-8), 56.1 (q, OMe-4), 60.9 (q, OMe-7), 94.5 (d, C-3), 107.2 (d, C-6), 110.3 (s, Ar), 118.5 (d, C-5), 132.6 (s, Ar), 133.6 (s, Ar), 153.3 (s, Ar), 164.1 (s, Ar), 164.6 (s, C=O); ms:  $m/z$  (relative intensity) 235 ( $\text{M}^+$ , 100), 220 (72), 206 (22), 192 (26), 189 (9), 119 (7).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}_4$ : C, 61.27; H, 5.57; N, 5.95. Found: C, 61.29; H, 5.38; N, 6.01.

#### 2,4-Dichloro-7,8-dimethoxyquinoline (12).

To a solution of 4-hydroxy-7,8-dimethoxy-2(1H)-quinolone **10** (1.26 g, 5.70 mmoles) and chlorobenzene (50 ml), phosphorus oxychloride (0.80 ml, 8.55 mmoles) and pyridine (0.14 ml, 1.71 mmoles) were added dropwise and the resulting mixture was refluxed for 2 hours. After evaporation of the solvent, a small amount of water was added to the residue and the residue was basified with saturated sodium carbonate solution and extracted with dichloromethane. The residue from the dichloromethane extract was chromatographed with chloroform to give 1.14 g (78%) of **12**. This compound was recrystallized from hexane to give colorless needles, mp  $134^\circ$ ; ir (potassium bromide): 3410, 1611, 1576, 1498, 1470, 1267, 1139, 1098, 993, 806  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  4.04 (3H, s, OMe-8), 4.11 (3H, s, OMe-7), 7.36 (1H, s, H-3), 7.41 (1H, d,  $J = 9.3$  Hz, H-6), 7.92 (1H, d,  $J = 9.3$  Hz, H-5);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  56.9 (q, OMe-8), 62.1 (q, OMe-7), 115.9 (d, C-6), 119.7 (d, C-5), 120.0 (d, C-3), 120.9 (s, Ar), 142.9 (s, Ar), 143.5 (s, Ar), 144.3 (s, Ar), 150.1 (s, Ar), 153.5 (s, Ar); ms: (FAB)  $m/z$  258 ( $\text{MH}^+$ ).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_9\text{NO}_2\text{Cl}_2$ : C, 51.19; H, 3.51; N, 5.43. Found: C, 51.39; H, 3.49; N, 5.73.

#### 2,4,7,8-Tetramethoxyquinoline (13).

2,4-Dichloro-7,8-dimethoxyquinoline **12** (0.53 g, 2.05 mmoles) was added to sodium methoxide (from sodium 0.47 g, 20.5 mmoles and methanol 40 ml) and the mixture was refluxed for 40 hours. The mixture was poured into cold water (200 ml) and the resulting precipitate was filtered and washed with water. This compound was recrystallized from hexane to give 0.4 g (78%) of **13** as colorless prisms, mp  $101-102^\circ$ ; ir (potassium bromide): 2940, 1621, 1490, 1356, 1275, 1213, 1108, 1069, 1037, 827, 776  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  3.97 (3H, s, OMe-4), 3.98 (3H, s, OMe-8), 4.09 (3H, s, OMe-2), 4.12 (3H, s, OMe-7), 6.11 (1H, s, H-3), 7.06 (1H, d,  $J = 9.0$  Hz, H-6), 7.76 (1H, d,  $J = 9.0$  Hz, H-5);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  53.3 (q, OMe-2), 55.6 (q, OMe-4), 56.9 (q, OMe-8), 61.3 (q, OMe-7), 89.0 (d, C-3), 110.9 (d, C-6), 115.1 (s, Ar), 117.3 (d, C-5), 142.3 (s, Ar), 142.3 (s, Ar), 152.9 (s, Ar), 163.7 (s, Ar), 164.2 (s, Ar); ms: (FAB)  $m/z$  250 ( $\text{MH}^+$ ).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}_4$ : C, 62.64; H, 6.07; N, 5.62. Found: C, 62.62; H, 6.18; N, 5.67.

#### Preparation of 4,7,8-Trimethoxy-2(1H)-quinolone (11) from 13.

2,4,7,8-Tetramethoxyquinoline **13** (0.2 g, 0.8 mmoles) in 5% hydrochloric acid (8 ml) was refluxed for 1 hour, cooled, basified with saturated sodium hydrogen carbonate solution and extracted with chloroform. The residue from chloroform extract was purified by mpls (ethyl acetate as eluent) to give 47 mg (25%) of **11**. The mp and ir spectrum of this compound coincided with those of the authentic sample.

#### 3-Formyl-4,7,8-trimethoxy-2(1H)-quinolone (Glycocitridine) (2).

The residue was purified by mpls (hexane:ethyl acetate = 2:1) to give 0.3 g (54%) of **2**. This compound was recrystallized from ethyl acetate to give colorless prisms, mp  $239-240^\circ$  dec; ir (potassium bromide): 3450, 3150, 3000, 2950, 1670, 1620, 1500, 1480, 1450, 1350, 1310, 1280, 1090, 1060, 990, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  3.96 (3H, s, OMe-7), 3.99 (3H, s, OMe-8), 4.16 (3H, s, OMe-4), 6.87 (1H, d,  $J = 9.0$  Hz, H-6), 7.74 (1H, d,  $J = 9.0$  Hz, H-5), 9.12 (1H, br s, NH), 10.44 (1H, s,

CHO);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  56.3 (q, OMe-8), 61.1 (q, OMe-7), 64.6 (q, OMe-4), 108.2 (d, C-6), 110.9 (s, Ar), 111.6 (s, Ar), 121.9 (d, C-5), 133.5 (s, Ar), 134.1 (s, Ar), 155.5 (s, Ar), 164.3 (s, Ar), 169.7 (s, C=O), 189.8 (s, CHO); ms: m/z (relative intensity) 263 ( $\text{M}^+$ , 61), 235 (97), 234 (100), 220 (27), 206 (52), 205 (73), 188 (41).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{13}\text{NO}_5$ : C, 59.31; H, 4.98; N, 5.32. Found: C, 59.18; H, 4.81; N, 5.19.

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