Synthesis of 5,6-Dimethoxyquinazolin-2(1*H*)-ones

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Synthesis of 5,6-dimethoxyquinazolin-2(1*H*)-one derivatives was the subject of investigations leading to the preparation of title compounds **11**, **13**, **14** and **26**. Target quinazolines **1** were synthesized in three ways; the route starting from *o*-vanillin *via* the intermediacy of 6-amino-2,3-dimethoxyacetophenone (**19**) was used for most of the preparative work. The unexpected formation of an acid-labile dimer of **13** was discovered and solid state ^{13}C nmr was used for structural assignment. The 5-methoxy substituent in these systems shows anomalous spectral characteristics and, in one case, was cleaved in acid media to **22**.

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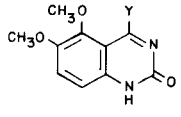
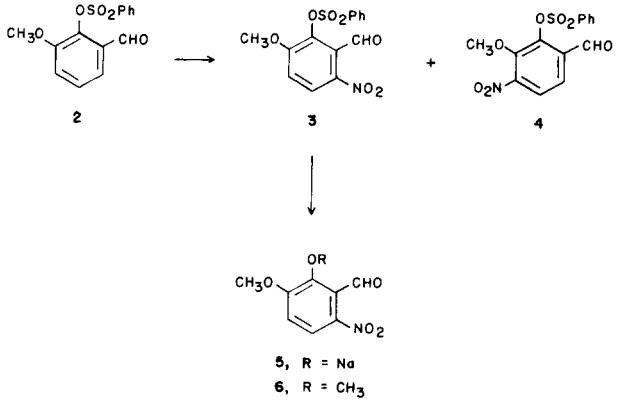
Quinazoline systems have been well studied both for chemical and pharmaceutical goals [1]. During the course of investigations seeking new cardiovascular agents, we began synthetic studies directed toward a series of novel quinazoline derivatives which might be useful as cardiotonic or renal vasodilatory agents [2,3]. Prior to this study, only a few substituted 5,6-dimethoxyquinazolines **1** had been reported and these systems became an important synthetic goal in our research programs [4].



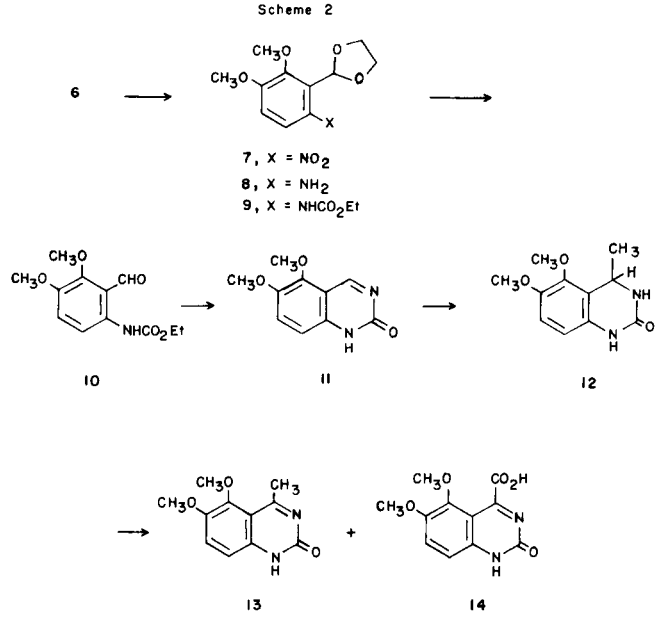
1, Y = alkyl, aryl

Scheme 1



Retrosynthetic analysis of **1** suggested that 2,3-dimethoxy-6-nitrobenzaldehyde (**6**) might be a useful intermediate for these studies. Although 2,3-dimethoxybenzaldehyde [4] could be nitrated according to the procedure of Robinson [5], *o*-vanillin was a more attractive precursor for **6** both because of its low cost and availability for large scale work. Preparation of **6** as outlined in Scheme 1 may be accomplished on a multimolar scale. Reaction of *o*-vanillin with benzenesulfonyl chloride was initially performed as described by Julia [6] to give **2** but, when run on large scale, unreacted benzenesulfonyl chloride proved very irritating. When excess *o*-vanillin and base were used, **2** could be prepared in 91% yield based on benzenesulfonyl chloride and the unreacted *o*-vanillin could be easily recovered. Nitration of **2** with 90% nitric acid at 0° gave a mixture of **3** and **4** [6] (approximately 2:1); the desired isomer **3** could be crystallized by treating the mixture with refluxing acetone. Although saponification of **3** could be accomplished with potassium hydroxide [6,7], the more dense sodium salt **5** was operationally superior since the resultant smaller bulk allowed a greater reaction throughput than was possible for the potassium salt. Methylation of **5** to **6** occurred easily in either DMF or acetone but, on larger scale, acetone was far easier to remove from the product. The methylation conditions described by Rosenthal

Scheme 2



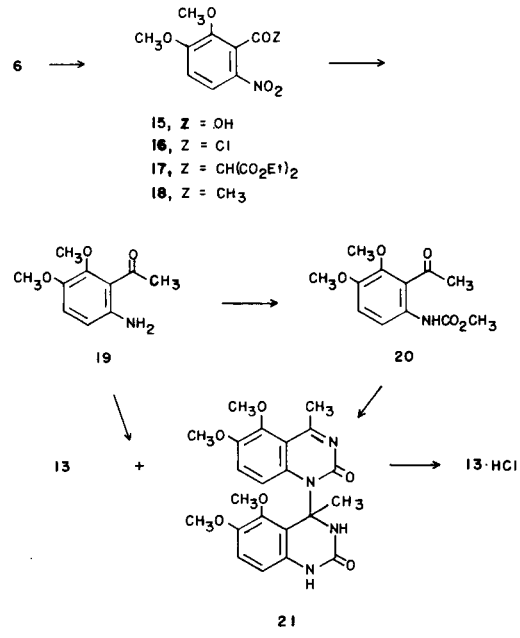
[8] (methyl iodide/silver oxide/chloroform) were far less satisfactory in terms of yield, convenience and expense.

With a reproducible, high yield source of **6**, synthesis of the target molecules **1** was approached as outlined in Scheme 2. To avoid self-condensation of the amino aldehyde formed by catalytic reduction of **6**, the aldehyde required protection as acetal **7**. Hydrogenation of **7** gave amine **8** nearly quantitatively and subsequent reaction with ethyl chloroformate provided carbamate **9** in good yield. Removal of the acetal protecting group with 0.1*N* hydrochloric acid in acetone gave the penultimate aldehyde carbamate **10** in good yield. Cyclization of **10** by treatment with ethanolic ammonia in an autoclave gave a moderate yield of **11**, the first member of the target 5,6-dimethoxyquinazoline system.

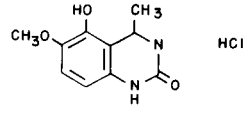
Quinazolinone **11** was sparingly soluble in most organic solvents but dissolved well in trifluoroacetic acid; the chemical shift of the 5-methoxy moiety at δ 4.45 was the only remarkable feature in the ^{1}H nmr of **11**. This unusual deshielding in ^{1}H nmr for the 5-methoxyl in the quinazolinones in this series (see also **13** and **14** below) may arise from steric compression by the buttressing effects of the 6-methoxyl and 4-substituent or from electronic effects caused by protonation by the strongly acidic solvent. Since ^{1}H nmr studies in dimethyl sulfoxide do not reveal this remarkable methoxyl shift, it most likely is caused by electronic effects. In spite of its low solubility, **11** reacted with methyl magnesium bromide in tetrahydrofuran to give dihydroquinazolinone **12** in excellent yield. Although oxidation of **12** with potassium permanganate gave only low yields of the easily separable 4-methyl **13** (5%) and 4-carboxy **14** (50%) derivatives, respectively, other routine oxidation procedures gave even less satisfactory results. As noted for **11**, both **13** and **14** also had unusual ^{1}H nmr absorptions for the 5-methoxyl moiety at δ 4.38 and δ 4.13, respectively.

In light of the interesting cardiovascular properties of **13** [3], an alternate route of synthesis was necessary for larger scale preparation of this material. As shown in Scheme 3, nitroaldehyde **6** was oxidized with potassium permanganate to give a high yield of acid **15** which was suitable for further reaction without purification. The acid was converted with thionyl chloride to acid chloride **16** which was reacted without further purification with the magnesium salt of diethyl malonate to give **17**. Although **17** could be purified, it was most expedient to decarboxylate the crude product with sulfuric acid to give the novel nitro acetophenone **18** in an overall 69% purified yield from **15**. Catalytic hydrogenation of **18** gave novel aminoacetophenone **19** quantitatively; **19** was isolable and stable in contrast to the hydrogenation product of **6**.

Scheme 3



Conversion of **19** to the desired **13** could be accomplished in either of two ways. Reaction of **19** with ethyl chloroformate gave carbamate **20** quantitatively. This compound was ring closed in an ammonium acetate melt at 125° to give a mixture of **13** and dimer **21** (*vide infra* for structural assignment) in 74% yield. More conveniently, **19** was converted directly to the same mixture of **13** and **21** by reaction with potassium isocyanate in acetic acid at 25° in essentially the same yield. When the mixture of **13** and **21** thus prepared by either route was dissolved in concentrated hydrochloric acid at 35° and subsequently diluted with water, the yellow monohydrochloride monohydrate of **13** crystallized from the solution in a 94% yield. The orange-red anhydrous hydrochloride salt of **13** could be prepared from the mixture with hydrogen chloride gas in acetic acid. The free base **13** was stable and could be isolated by neutralization of the hydrochloride salt.



22

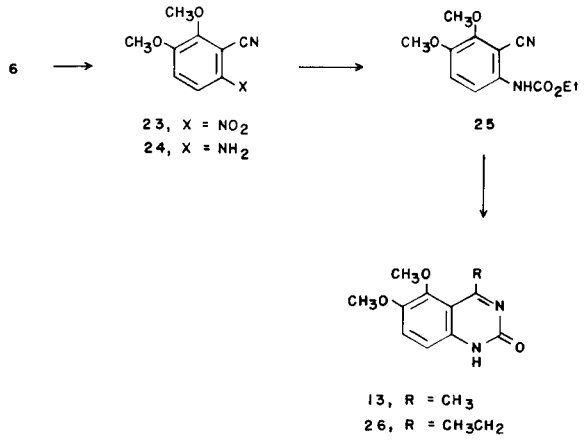
While the treatment of the ring closure mixture of **13** and **21** with hydrochloric acid eliminated the presence of the dimer **21**, the strong acid and elevated temperatures (75-85°) used initially created another impurity. This prolonged acid exposure caused the production of demethylated derivative **22**. Combustion, mass spectral and ^{1}H nmr analyses all indicated loss of one methyl group. The struc-

ture of **22** was initially assigned based upon the absence of the previously noted unusual ^{1}H nmr absorption at δ 4.4 for the 5-methoxy noted for in **11**, **13** and **14**. Since the chemistry of the 5-methoxy group might also reflect the previously mentioned steric effects, acid catalyzed hydrolysis at this site might be quite facile. Further support for the position of demethylation on **22** was obtained from the larger pyridine-induced shift of the 4-methyl in the ^{1}H nmr of **22** (δ 3.19 *vs* δ 2.76 in deuteriodimethyl sulfoxide for a change of +0.43 ppm) compared to that for **13** (δ 2.94 *vs* δ 2.76 for a change of +0.18 ppm). The larger shift in pyridine supports a 5-hydroxy group coordination with pyridine and a concomitant shift in 4-methyl absorption. Formation of **22** could be completely prevented by maintaining temperatures below 35° during the hydrochloric acid treatment.

The more surprising result was the formation of dimer **21**. This dimer was isolated in reasonably pure form when the mixture of **13** and **21** was treated with 6*N* hydrochloric acid, whereupon **13** dissolved and **21** could be isolated by rapid filtration. This material (**21**) is rapidly converted by acid to form **13** and was characterized as isolated without further purification since it coelutes with **13** on chromatographic supports such as silica gel or alumina. Infrared analysis of **21** showed a strong very broad absorbance at 1700 cm^{-1} (compared to 1660 cm^{-1} for **13**). This compound was refractory to usual mass spectral techniques, thermally degrading to **13** under electron impact. An ion at m/z 440 was observed by negative electron capture desorption chemical ionization, with a major fragment at m/z 220 suggestive of a dimeric species.

Routine nmr analysis was precluded by the insolubility of **21** in customary nmr solvents (other than trifluoroacetic acid which causes an immediate reversion to **13**) and therefore a solid state ^{13}C nmr spectrum was obtained for both **13** and **21**. Carbon assignments for **13** were first made using additivity relationships and direct long range ^{13}C-^{1}H couplings from gated decoupled spectra obtained in solution (Table 1). As may be seen from the solid state data (Table 2), there is close agreement between the solid and solution chemical shifts which allowed assignment of solid state resonances. The asymmetric doublets for C-2 and C-9 and the broadening of the C-4 resonances are readily attributed to residual ^{14}N-^{13}C dipolar coupling in the solid state [9]. Comparison of the solid state data for **21** and **13** shows that all the peaks for **13** are contained in **21** and, in most cases, in duplicate (*cf.* C-2, -5, -6, -7 and -9), suggestive of a dimeric structure. The most notable difference between the two spectra is the appearance of the C-4 and C-4′ methyl peaks at 47 ppm and 61 ppm in **21**. The essentially unchanged C-4 methyl at 27 ppm is further suggestive of a dimeric structure bonded between N-1 of one monomeric unit (accounting for the 47 ppm shift) and C-4 of the other monomeric unit (accounting for the C-4 methyl at 27 ppm). These data as well as the facile acid catalyzed conversion of **21** to monomeric **13** support the structural assignment.

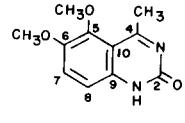
Scheme 4



In further work, an additional method of synthesis of quinazolines **1** has also been developed which involves far fewer manipulations (Scheme 4). In this approach aldehyde **6** is converted essentially quantitatively by the method of Olah [10] to the nitrile **23**. Catalytic reduction of **23** gave amine **24** in 88% yield. The carbamate **25** was prepared in 77% yield from the amine. Reaction of **25** with Grignard reagents led unexpectedly to the direct addition/ring-closed product without isolation of the imine and/or ketone intermediate. This is the first example to our knowledge of this type of direct ring closure trapping to give quinazolinones. Thus, when **25** was reacted with ethyl Grignard reagent, 4-ethyl derivative **26** was isolated

Table 1

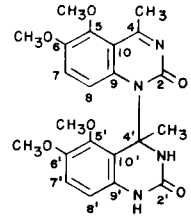
^{13}C NMR Solution Data for **13**



Carbon	Chemical Shift (ppm) deuteriochloroform
2	157
4	176
5	147
6	147
7	122
8	111
9	137
10	111
C-4 Methyl	28
C-5 Methoxy	61
C-6 Methoxy	57

Table 2

^{13}C NMR Solid State Data for **13** and **21**



13		**21**	
Carbon	Chemical Shift (ppm)	Carbon	Chemical Shift (ppm)
4	174 (br)	4	174 (br)
5	147	5,5′	147 (d, J = 95 Hz)
6	145	6,6′	144 (d, J = 92 Hz)
2	157 (d, J = 93 Hz)	2,2′	156 (m)
9	137 (d, J = 104 Hz)	9,9′	138 (d, J = 127 Hz)
			131 (d, J = 147 Hz)
7	118	7,7′	119, 121
8, 10	111	8,8′, 10,10′	110
		4′	61
C-5 Methoxy	59	C-5,5′ Methoxy	59
C-6 Methoxy	57	C-6,6′ Methoxy	54
		C-4′ Methyl	47
C-4 Methyl	30	C-4 Methyl	27

in 11% yield. In a similar way, reaction of **25** with methyl magnesium bromide gave **13** in 11% yield. The use of dioxane as a solvent was required for this latter reaction. While these yields are low, the ready access to numerous possible substitutions at the 4-position make this method of synthesis of 5,6-dimethoxyquinazolinones very attractive for synthesis of additional analogues in this system.

EXPERIMENTAL

Melting point determinations were done on either a Mel-Temp or Thomas Hoover capillary apparatus and are uncorrected. All compounds were homogeneous by thin layer chromatographic analysis using Analtech silica gel GF uniplates. The ^{1}H nmr solution spectra were obtained on a Varian T-60A spectrometer in chloroform-d, trifluoroacetic acid or deuterio dimethyl sulfoxide. The ^{13}C nmr solution spectra were measured in chloroform-d at 100 MHz on a Varian Associates XL-400 spectrometer. The spectrum was acquired at ambient temperatures using a spectral width of 20 KHz using 30K data points giving a spectral resolution of 0.25 Hz/data point. The ^{13}C solid state cross-polarization magic-angle spinning (CP/MAS) spectra were measured at 37.735 MHz at ambient temperature on a Nicolet NT-150 spectrometer with a homebuilt CP/MAS unit including the probe. The cross-polarization contact time was 2 ms and the repetition time was 2 seconds. The decoupling field was 55 KHz. The samples were spun at 3800 rps and sample volume was 3 ml. The spectra were measured at 20 KHz spectral width using 2K data points giving a resolution of 9.8 Hz/point. All chemical shifts are relative to external tetramethylsilane. Electron impact (EI) mass spectral data were obtained on a Finnigan 1015 quadrupole mass spectrometer with an electron energy of 20 eV. The electron capture desorption negative chemical ionization mass spectral data were obtained on a Finnigan-MAT 8230 BE double focusing mass spectrometer.

2-Hydroxy-3-methoxybenzaldehyde Benzenesulfonate (**2**).

A solution of *o*-vanillin (**1**, 537.5 g, 3.54 moles) in water (3.6 liters) containing potassium hydroxide (215 g, 3.77 moles) was treated with benzenesulfonyl chloride (360 ml, 2.83 moles) dropwise over a period of 1 hour. Methylene chloride (75 ml) was added and the mixture was stirred overnight. The resultant solid was collected by filtration and washed with 500 ml of 5% aqueous potassium hydroxide and 1 liter of water. The solid was dried *in vacuo* at 70-90° to give **2**, 750 g (91% based upon benzenesulfonyl chloride), mp 115-119° which was suitable for nitration. Unreacted *o*-vanillin could be recovered from the filtrates by acidification and extraction. Recrystallization of a sample of **2** from methylene chloride or acetone gave the analytical sample, mp 119-121°, lit [6] mp 119-120°.

Anal. Calcd. for $C_{14}H_{12}SO_5$: C, 57.54; H, 4.14. Found: C, 57.45; H, 4.14.

2-Hydroxy-3-methoxy-6-nitrobenzaldehyde Benzenesulfonate (**3**).

Benzenesulfonate **2** (200 g, 0.685 mole) was added to 90% nitric acid (440 ml) with temperature maintained at 0° ±2° over a period of 0.5 to 1 hour. The reaction mixture was stirred an additional 0.5 hour and poured over ice (2.5 liters) with stirring. After standing several hours, the solid was collected by filtration and washed with water (500 ml). The solid was suspended in acetone (1.25 liters) and the mixture was heated to reflux for 0.5 hour, concentrated to 500 ml and cooled to 15°. The resultant solid was collected by filtration and washed with cold acetone (125 ml) to provide pure **3**, 138.5 g (60%), mp 151-155°, lit [6] mp 152-154°.

This nitration gives a 2:1 ratio of **3**:**4** as evidenced by ^{1}H nmr analysis. No attempt to isolate pure **4** was made.

Caution: During the nitration, if the reaction temperature rose to 8-15°, a vigorous exotherm occurred and the reaction mixture could not be contained in the flask.

2-Hydroxy-3-methoxy-6-nitrobenzaldehyde, Sodium Salt (**5**).

Nitrobenzenesulfonate **3** (120.8 g, 0.358 mole) was added to methanol (1.6 liters) and the mixture was heated to 50° with vigorous stirring. Sodium hydroxide (66.1 g) in water (66 ml) was added at a rate to raise and maintain reflux temperature. A copious orange precipitate formed

which interfered with stirrring. The reaction was heated to reflux for an additional 0.5 hour and cooled to room temperature. The solid was collected by filtration, washed with methanol and acetone and air dried to give **5**, 75.2 g (95%), mp >300°.

When potassium hydroxide was used in this saponification, the vermillion salt formed in the same yield but the product was twice as voluminous and this increased bulk reduced batch capacity.

2,3-Dimethoxy-6-nitrobenzaldehyde (**6**).

Sodium salt **5** (130.0 g, 0.593 mole) was slurried in acetone (1.3 liters) containing potassium carbonate (130 g) and the suspension was treated with dimethylsulfate (127 g, 1.0 mole) and heated to reflux for 3.5 days. After standing for an additional 24 hours, the salts were removed by filtration and the filtrate was concentrated and the residue recrystallized from isopropanol to give **6** (103.5 g, 83%, mp 108.5-109.5° lit [8] mp 109-110.5°) as a pale yellow solid.

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 50.94; H, 4.37; N, 6.47.

2,3-Dimethoxy-6-nitrobenzaldehyde Ethylene Acetal (**7**).

A mixture of **6** (16.0 g, 75 mmoles), ethylene glycol (64 g, 103 mmoles), and *p*-toluenesulfonic acid monohydrate (0.2 g) in benzene (750 ml) was heated to reflux with a Dean-Stark apparatus for 48 hours (2.6 ml of water was collected). The solution was then poured into water (1 liter). The organic phase was washed with aqueous saturated sodium bicarbonate (2 x 20 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The crude product was recrystallized from hexanes (2 liters) to give **7** (15.2 g, 78%, mp 74-76°; ^{1}H nmr (deuteriochloroform): δ 7.36 (d, 1H, Ar-4-*H*), 6.86 (d, 1H, Ar-5-*H*), 6.20 (s, 1H, -C*H*), 4.05 (d, 4H, J = 3.0 Hz, OCH_2), 3.90 (s, 3H, 2-OCH_3), 3.86 (s, 3H, 3-OCH_3); ms: m/z 255 (M^+).

Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.85; H, 5.27; N, 5.42.

6-Amino-2,3-dimethoxybenzaldehyde Ethylene Acetal (**8**).

A solution of **7** (39.12 g, 0.153 mole) in ethyl acetate (350 ml) was treated with sodium acetate (1.2 g) and platinum oxide (2.45 g) and hydrogenated on a Parr apparatus at 50 psi for 1 day. The reaction mixture was filtered and the filtrate was concentrated to a brown syrup, 33.23 g (96%) which was crystallized from hexanes to give a tan solid, mp 78°-80°. This material was converted to the carbamate **9** without additional purification; ^{1}H nmr (deuteriochloroform): δ 6.78 (d, 1H, Ar-4-*H*), 6.35 (d, 1H, Ar-5-H), 6.19 (δ, 1H, -C*H*), 4.10 (m, 4H, OCH_2), 3.85 (s, 3H, 2-OCH_3), 3.80 (s, 3H, 3-OCH_3); ms: m/z 225 (M^+).

6-(*N*-Carboethoxyamino)-2,3-dimethoxybenzaldehyde Ethylene Acetal (**9**).

Ethyl chloroformate (1.9 g, 17.5 mmoles) was added with stirring to **8** (1.6 g, 7.1 mmoles) dissolved in tetrahydrofuran (50 ml). An exothermic reaction occurred and a solid formed instantly. A solution of sodium hydroxide (0.72 g in 3.5 ml water) was added and the solution stirred for 2 hours at room temperature. Tetrahydrofuran was removed *in vacuo* and the residue extracted with chloroform (2 x 100 ml), dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The crude product was recrystallized from hexanes to afford **9** (1.2 g, 57%) mp 95°-96°; ^{1}H nmr (deuteriochloroform): δ 8.06 (bs, 1H, NH), 7.76 (d, 1H, Ar-4-*H*), 6.90 (d, 1H, Ar-3-*H*), 6.15 (s, 1H, -C*H*), 3.83 (s, 6H, OCH_3), 3.93-4.40 (m, 6H, COCH_2, CH_2O), 1.3 (t, 3H, CH_3); ms: m/z 297 (M^+).

Anal. Calcd. for $C_{14}H_{19}NO_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.34; H, 6.28; N, 7.54.

6-(*N*-Carboethoxyamino)-2,3-dimethoxybenzaldehyde (**10**).

Compound **9** (5.0 g, 16.8 mmoles) was dissolved in acetone (36 ml) and hydrochloric acid (3 ml). The mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo* to give a yellow solid (3.9 g). Recrystallization from hexanes gave pure **10** as a yellow solid; 3.6 g (85%), mp 86-88°; ^{1}H nmr (deuteriochloroform): δ 10.50 (bs, 1H, N*H*), 10.40 (s, 1H, C*H*O), 8.10 (d, 1H, Ar-4-*H*), 7.16 (d, 1H, Ar-3-*H*), 4.20 (q, 2H, J = 7.0 Hz, CH_2), 4.00 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 5-OCH_3), 1.30 (t, 3H, J = 7.0 Hz, CH_3); ms: m/z 251 (M^+).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.91; H, 6.01; N, 5.54.

5,6-Dimethoxyquinazoline (**11**).

Ammonia was bubbled into ethanol (1 liter) cooled to dry ice bath temperature for 1 hour. Compound **10** (45.12 g, 0.178 mole) was added and the resultant solution was heated to 130° in an autoclave for 6 hours. The brown solution was treated with charcoal, filtered and the filtrate was concentrated to 300 ml. A yellow solid precipitated upon cooling which was collected by filtration and dried at 100° *in vacuo* to give **11**, 19.65 g (54%), mp 242-244°; ^{1}H nmr (trifluoroacetic acid): δ 10.80 (s, 1H, N*H*), 8.15 (d, 1H), 7.30 (d, 1H, both Ar*H*), 4.45 (s, 3H, 5-CH_3O), 4.05 (s, 3H, 6-CH_3O); ms: m/z 206 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.13; H, 5.33; N, 14.02.

3,4-Dihydro-5,6-dimethoxy-4-methyl-2(1*H*)-quinazolinone (**12**).

To a suspension of **11** (10.0 g, 48.5 mmoles) in dry tetrahydrofuran (1.1 liters) under nitrogen, was added at 0° over 20 minutes, an excess of methyl magnesium bromide in ether (62.60 ml of a 3.1 *M* solution in ether, 194.0 mmoles). Upon addition of the MeMgBr, most solids dissolved (a fine tan solid was present throughout the course of the reaction). The reaction mixture was removed from the cooling bath and allowed to reach room temperature and was stirred for 16 hours. Additional MeMgBr was added (15.66 ml of a 3.1 *M* solution in ether, 48.5 mmoles and the reaction mixture was heated to reflux for 2 hours. The reaction mixture was cooled with an ice-water bath and aqueous ammonium chloride (100 ml of saturated solution diluted with 100 ml of water) was added with stirring. After the addition was complete, 10% hydrochloric acid was added to achieve a *p*H of 6.0. The layers were separated and the aqueous layer was extracted with chloroform (3 x 250 ml). The chloroform extract was combined with the previously separated tetrahydrofuran layer, and the combined organic layers were washed with saturated brine (200 ml) and dried over sodium sulfate. Concentration of the organic layer to 250 ml produced an off-white precipitate which was collected by filtration and recrystallized from isopropanol (200 ml) to give **12** as a colorless solid, 9.47 g (88%), mp 210-212°; ^{1}H nmr (trifluoroacetic acid): δ 8.90 (broad s, 1H, N-*H*), 6.80-7.35 (m, 2H, Ar *H*), 4.80-5.50 (m, 1H, 4-*H*), 3.60-4.50 (m, 6H, OCH_3), 1.60 (d, 3H, 4-CH_3); ms: m/z 222 (M^+).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.08; H, 6.39; N, 12.47.

5,6-Dimethoxy-4-methyl-2(1*H*)-quinazolinone (**13**) and (5,6-Dimethoxy-2(1*H*)-quinazolinon-4-yl)carboxylic Acid (**14**).

Potassium permanganate (25.66 g, 162.38 mmoles) was added to a solution of **12** (18.04 g, 81.19 mmoles) in acetone (5.0 liters) and the mixture was stirred at room temperature (under nitrogen, protected from light with aluminum foil) for 96 hours. The brown precipitate was collected by filtration and washed with acetone (500 ml). The filtrate was concentrated to give recovered **12** (4.65 g, 21%). The brown precipitate was triturated with boiling water (1 liter) and the solution was decanted, and neutralized with 10% hydrochloric acid. Extraction with chloroform (4 x 250 ml) and 10% 2-propanol/ethyl acetate (4 x 250 ml), and concentration of the aqueous layer to dryness *in vacuo* afforded 8.20 g of **14**. The 2-propanol/ethyl acetate layer was concentrated to give additional 1.30 g of **14**. The chloroform extracts were dried over magnesium sulfate, filtered, and concentrated to 500 ml wherein a precipitate formed. Filtration and drying afforded 0.65 g additional **14** (total yield = 10.15 g, 50%). The filtrate was further concentrated *in vacuo* to give 3.25 g of a tan solid consisting of approximately equal amounts of **13** and **14** which was separated on a 350 g SilicAR column that had been prepared in chloroform.

Elution with 0.5% methanol in chloroform afforded **13** as a yellow solid (1.92 g, 11%). Recrystallization from 2-propanol (75 ml) afforded **13** as a yellow solid, 0.94 g (5.3%), mp 230-232; ^{1}H nmr (trifluoroacetic acid): δ 8.0 (d, 1H), 7.35 (d, 1H, Ar-*H*), 4.38 (s, 3H, 5-OCH_3), 4.05 (s, 3H,

6-OCH_3), 3.38 (s, 3H, 4-CH_3); ms: m/z 220 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.76; H, 5.51; N, 12.19.

Recrystallization of **14** from acetone gave an analytical sample, mp 267-269°; ^{1}H nmr (trifluoroacetic acid): δ 9.76 (bs, 1H, -CO_2H), 7.63 (d, 1H), 7.21 (d, 1H, Ar-*H*), 4.13 (s, 3H, 5-OCH_3), 4.05 (s, 3H, 6-OCH_3); ms: m/z 251 (MH^+).

Anal. Calcd. for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 53.12; H, 4.27; N, 11.96.

2,3-Dimethoxy-6-nitrobenzoic Acid (**15**).

Aldehyde **5** (40.0 g, 0.19 mole) was treated with acetone (275 ml) and warmed to 50°. A solution of potassium permanganate in water (60 g/liter) was added slowly at a rate to maintain 45° over a period of 16-20 hours until thin layer chromatographic analysis revealed complete absence of **5** (approximately 750-800 ml of oxidant solution was consumed). 2-Propanol (7.5 ml) was then added and the mixture was heated an additional hour. The precipitated manganese dioxide was removed by filtration and the filter cake was washed with 3% aqueous potassium hydroxide (*ca* 175-200 ml). The combined filtrates were acidified with hydrochloric acid and the precipitate was collected by filtration and dried *in vacuo*. The crude **6** was recrystallized from acetone to give the pure material, 28.3 g (67%), mp 187-189°, lit [4] mp 186-189°.

Anal. Calcd. for $C_9H_9NO_6$: C, 47.58; H, 4.00; N, 6.17. Found: C, 47.58; H, 3.96; N, 6.08.

Diethyl 2-(2,3-Dimethoxy-6-nitrobenzoyl)propanedioate (**17**).

Acid **15** (25 g, 0.11 mole) was added to thionyl chloride (50 ml) and the mixture was heated to reflux for 3 hours. Excess thionyl chloride was removed by distillation and the residue was triturated with toluene (50 ml) and again solvent was removed by distillation. It was essential to remove all traces of thionyl chloride. Acid chloride **16** was dissolved in toluene (40 ml) and diethyl ether (40 ml). The toluene was found necessary for crystallization in the next step.

Grignard quality magnesium (3.04 g, 0.125 mole) was treated with absolute ethanol (3.1 ml) and carbon tetrachloride (0.5 ml) and diethyl ether (100 ml) was added once vigorous reaction began. A solution of diethyl malonate (23.4 g, 0.146 mole) in ether (18 ml) and ethanol (14 ml) was added over 1 hour to maintain reflux. The mixture was heated to reflux an additional 3 hours. The reaction solution was then diluted with toluene (40 ml) and ether (80 ml).

The acid chloride **16** solution from above was added to the magnesium salt solution over a period of 0.5 hour at reflux and the entire mixture was heated an additional 3 hours. After cooling to 15°, the precipitate was collected by filtration; this solid was then added to 10% sulfuric acid (125 ml) and the resultant aqueous solution was extracted with methylene chloride. The methylene chloride layers were dried over magnesium sulfate and concentrated to give diester **17**, 39.1 g (96%), mp 71-73°. This material was used without purification in the next step.

An analytical sample of **17** was prepared from methanol, mp 73-73.5°; ^{1}H nmr (deuteriochloroform): δ 14.5 (s, 1H, enol O*H*), 8.1 (d, 1H), 7.1 (d, 1H, both Ar*H*), 4.02 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 4.1 (m, 4H, CH_2), 1.12 (t, 3H, CH_3), 0.89 (t, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{19}NO_9$: C, 52.03; H, 5.18; N, 3.79. Found: C, 52.27; H, 5.22; N, 3.80.

2,3-Dimethoxy-6-nitroacetophenone (**18**).

Diester **17** (39.1 g, 0.106 mole) was heated to reflux in 60% aqueous acetic acid (60 ml) containing sulfuric acid (4.25 ml) for 7 hours. Aqueous sodium hydroxide (4 g in 8 ml of water) was added slowly with cooling and the solution was concentrated to an oil. This residue was dissolved in methylene chloride, decolorized with charcoal, evaporated and recrystallized from 2-propanol to give acetophenone **18**, 22.5 g (100%), mp 66-67°; ^{1}H nmr (deuteriochloroform): δ 7.95 (d, 1H), 6.98 (d, 1H, both Ar*H*), 4.02 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3); ms: m/z 225 (M^+).

Anal. Calcd. for $C_{10}H_{13}NO_5$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.33; H, 6.92; N, 7.11.

6-Amino-2,3-dimethoxyacetophenone (**19**).

Nitroketone **18** (20.0 g, 0.089 mole) dissolved in methanol (100 ml) containing 10% palladium-carbon catalyst (0.5 g) was hydrogenated with cooling in a Parr apparatus. The catalyst was removed by filtration, the filtrate concentrated and the residue was recrystallized from isopropanol to give **19**, 16.25 g (94%), mp 60-60.5°; ^{1}H nmr (deuteriochloroform): δ 6.92 (d, 1H), 6.35 (d, 1H, both Ar*H*), 5.15 (brs, 2H, NH_2), 3.88 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.6 (s, 3H, CH_3); ms: m/z 195 (M^+).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.33; H, 6.92; N, 7.11.

6-Carboethoxyamino-2,3-dimethoxyacetophenone (**20**).

Amine **19** (48.0 g, 0.246 mole) dissolved in tetrahydrofuran (370 ml) was treated with ethyl chloroformate (59.1 ml) over a period of 1 hour at 0°. After 30 minutes, a solution of sodium hydroxide (22.9 g) in water (85 ml) was added to the mixture over 30 minutes. After additional stirring for 1 hour, the mixture was filtered, and the upper layer of the filtrate was separated and evaporated *in vacuo*. The lower layer of the filtrate was extracted with methylene chloride and this phase was added to the residue from the upper layer. Concentration and recrystallization of the residue from isopropanol/hexanes gave pure **20**, 65.9 g (100%), mp 63-65°; ^{1}H nmr (deuteriochloroform): δ 8.83 (brs, 1H, N*H*), 7.80 (d, 1H), 7.02 (d, 1H, both Ar*H*), 4.1 (q, 2H, CH_2), 3.91 (s, 3H, OCH$_3$), 3.88 (s, 3H, OCH$_3$), 2.63 (s, 3H, COCH_3), 1.33 (t, 3H, CH_3); ms: m/z 267 (M^+).

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.29. Found: C, 58.36; H, 6.42; N, 5.19.

5,6-Dimethoxy-4-methyl-2(1*H*)-quinazolinone (**13**) from **19**.

Amine **19** (100 g, 0.513 mole) was dissolved in glacial acetic acid (2 liters) and was treated with a filtered solution of potassium cyanate (50 g) in water (200 ml) over 1 hour with cooling to maintain the reaction temperature <25°. The mixture was stirred overnight and the precipitate was collected by filtration; the solid was washed with water until the filtrate was colorless and acetone until the filtrate was colorless. Drying *in vacuo* gave a light yellow solid mixture of **13** and **21**, 107.2 g (95%).

This solid was dissolved in concentrated hydrochloric acid (1.1 liters) at 35°, filtered, diluted with water (6.2 liters) and stored at 5° for 12 hours. The golden yellow solid was collected by filtration, washed with acetone (600 ml) and air dried to give **13**·HCl·H_2O 118 g (94%), mp 208-210°; ^{1}H nmr (trifluoroacetic acid): δ 8.01 (d, 1H), 7.37 (d, 1H, both Ar*H*), 4.38 (s, 3*H*, 5-CH_3O), 4.08 (s, 3H, 6-CH_3O), 3.40 (s, 3H, CH_3); ms: m/z 220 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$·HCl·H_2O: C, 48.09; H, 5.50; N, 10.20. Found: C, 48.00; H, 5.29; N, 10.05.

The solid mixture of **13** and **21** (5.08 g, 0.023 mole) was dissolved in refluxing acetic acid (50 ml) and treated with hydrogen chloride bubbled through the solution for 10 minutes. The reaction mixture was allowed to cool to 50°, filtered and the collected red orange solid was washed with acetic acid, acetone and ether to give **13**·HCl, 5.2 g (88%), mp 207-209°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$·HCl: C, 51.47; H, 5.10; N, 10.91. Found: C, 51.43; H, 5.06; N, 11.06.

The hydrochloride of **13** (4.26 g) was dissolved in water (500 ml) and 30% aqueous sodium hydroxide solution was added to adjust the *p*H of the solution to 7. The yellow crystalline solid was collected by filtration, washed with acetone and dried to give **13** (3.40 g, 100%), mp 241-244°; ir (potassium bromide): 1660 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.64; H, 5.41; N, 12.57.

13 from **20**.

Carbamate **20** (65.9 g, 0.246 mole) was placed in a flask, covered with ammonium acetate (365 g) and the mixture was heated in an oil bath un-

til a clear melt was obtained. Stirring and heating of the melt at 125-130° for 2 hours followed by quenching of the molten reaction in 2 liters of water gave a solid (a mixture of **13** and **21**, 40 g, 74%) after drying of the filtered precipitate. Treatment of the mixture with hydrochloride acid as described above gave the hydrochloride salt of **13** as a hydrate.

5-Hydroxy-6-methoxy-4-methyl-2(1*H*)-quinazolinone Hydrochloride (**22**) and Isolation of **21**.

A mixture of **13** and **21** (837 g) was treated with 6*N* hydrochloric acid (20 liters) at 110° and quickly filtered. The tan solid (25 g) was predominantly **21** as judged by spectral analysis (Table 2), mp 241-247°; ir (potassium bromide): 1700, 1660 cm^{-1}; ms: (positive DCI) m/z 221 (MH^+); ms: (negative electron capture DCI) m/z 440 ($M^{\bullet-}$). Attempts to further purify **21** failed probably to its facile conversion to **13**.

Anal. Calcd. for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.08; H, 5.79; N, 12.44.

The filtrates were allowed to cool and the solid **13** hydrochloride hydrate (363 g) was collected by filtration. The filtrate was reheated, concentrated and cooled to 15° and additional **13** hydrochloride hydrate (482 g) was collected by filtration.

This filtrate was concentrated with heat to a total volume of 6 liters, cooled to 5° and a red and yellow solid was collected (60 g). Red crystalline **22** hydrochloride precipitated from the filtrate upon standing an additional week and was collected by filtration (9 g). Recrystallization from methanol gave the analytical sample, mp 288-293°; ^1H nmr (trifluoroacetic acid): δ 7.40 (d, 1H), 6.67 (d, 1H, both Ar*H*), 3.6 (s, 3H, CH_3O), 2.95 (s, 3H, CH_3); ms: m/z 206 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_2O_3 \cdot HCl$: C, 49.32; H, 4.56; N, 11.51. Found: C, 49.04; H, 4.63; N, 11.25.

2,3-Dimethoxy-6-nitrobenzonitrile (**23**).

Benzaldehyde **6** (15.0 g, 0.071 mole) and hydroxylamine hydrochloride (6.42 g, 0.097 mole) were mixed in formic acid (200 ml) and heated to reflux for 2 hours. The mixture was cooled to room temperature and quenched with 1.5 liters of ice water. Solid potassium hydroxide was added to alkalinity and the precipitate was collected by filtration, washed with water and air dried to give **23** (14.2 g, 96%).

A sample (2.2 g) was recrystallized from methanol to give the analytical sample (1.9 g), mp 165-166°; ir (potassium bromide): 2240 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.97 (d, 1H), 7.05 (d, 1H, both Ar*H*), 4.05, 4.00 (2s, 6H, CH_3O); ms: m/z 208 (M^+).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.69; H, 3.73; N, 13.45.

6-Amino-2,3-dimethoxybenzonitrile (**24**).

A suspension of iron powder (8.7 g, 0.156 mole) and nitrobenzonitrile **23** (9.3 g, 0.0445 mole) in glacial acetic acid (30 ml) and 2-propanol (30 ml) was heated to 75° and the heat source was removed. The reaction mixture began to reflux spontaneously for 5 minutes. The heat source was reapplied to maintain reflux for an additional hour. The reaction mixture was treated with activated charcoal (10 g), filtered hot and the collected solids washed with hot isopropanol. The filtrate was evaporated *in vacuo*, the residue was dissolved in chloroform (200 ml) and the organic layer was washed with 5% sodium bicarbonate solution (100 ml) and dried over sodium sulfate. The solvent was evaporated *in vacuo* to give amino benzonitrile **24** (7.0 g, 88%) as a red oil; ^1H nmr (deuteriochloroform): δ 6.95 (d, 1H), 6.37 (d, 1H, both Ar*H*), 4.15 (brs, 2H, NH_2), 3.98, 3.77 (2s, 6H, CH_3O); ms: m/z 178 (M^+).

6-(*N*-Carbomethoxyamino)-2,3-dimethoxybenzonitrile (**25**).

A mixture of amine **24** (9.9 g, 55.6 moles), methylchloroformate (21.5 ml, 0.278 mole) and sodium bicarbonate (3.84 g, 0.0278 mole) in chloroform (100 ml) was heated to reflux for 2 hours. The inorganic materials were removed by filtration, and the filtrate was evaporated *in vacuo* to give a solid which was recrystallized from methanol to give carbamate **25** (9.55 g, 73%) as a colorless solid mp 143-144°; ^1H nmr (deuteriochloroform): δ 7.70 (d, 1H), 7.05 (d, 1H, both Ar*H*), 6.88 (brs, 1H, N*H*), 3.98 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CH_3), 3.77 (s, 3H, CH_3); ms: m/z 236 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.07; H, 5.21; N, 11.73.

5,6-Dimethoxy-4-ethyl-2(1*H*)-quinazolinone (**26**).

Ethyl magnesium bromide (30.9 ml of a 2*N* solution in tetrahydrofuran, 0.061 mole) was added *via* syringe to dry tetrahydrofuran (150 ml) and the solution was cooled in an ice bath. Carbamate **25** (7.3 g, 0.031 mole) in dry tetrahydrofuran (100 ml) was added dropwise to the cooled Grignard reagent. The reaction mixture was warmed to room temperature for 2 hours, recooled and ice water (50 ml) was added. Sulfuric acid (1*N*, 10 ml) was added and the mixture was stirred for 3 days. Solvent was removed *in vacuo* without heat and the aqueous residue was extracted with ether and with chloroform. The organic layers were dried over sodium sulfate. The aqueous layer was neutralized with 5% aqueous sodium bicarbonate and the resultant solid was collected by filtration and combined with the dried organic extracts. Concentration and recrystallization of the solid from ethanol gave **26** as a yellow solid, 0.80 g (11%) mp 224-226°; ^1H nmr (trifluoroacetic acid): δ 8.6 (d, 1H), 7.36 (d, 1H, both Ar*H*), 4.40 (s, 3H, 5-CH_3O), 4.05 (s, 3H, 6-CH_3O), 3.6 (m, 2H, CH_2), 1.66 (t, 3H, CH_3); ms: m/z 234 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_3 \cdot 1/4H_2O$: C, 60.43; H, 6.02; N, 11.24. Found: C, 60.35; H, 6.15; N, 11.62.

13 from **25**.

Methyl magnesium bromide (9.4 ml of a 2.85 *N* solution in ether, 0.027 mole) was added to dry dioxane (50 ml) and the solution was cooled with stirring in an ice bath. A solution of carbonate **25** (2.3 g, 0.0092 mole) was added dropwise and the mixture was heated to reflux for 4 hours. After the mixture was cooled to room temperature, water (10 ml) was added followed by 1*N* sulfuric acid (3 ml) and stirring was continued for 2 hours. Solvent was removed *in vacuo* at room temperature and the residue was triturated with water (50 ml). A crystalline solid which was shown to be unreacted **25** formed and was collected by filtration. The filtrate was extracted with chloroform (100 ml) and the organic layer was washed with 5% sodium bicarbonate solution (25 ml) and water (25 ml), dried over sodium sulfate and concentrated to give an oily solid. Trituration with ether and then isopropanol gave **13** (0.21 g, 11%), mp 239-241° which was identical in all respects to **13** described above.

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