Quino[1,2-*c*]quinazolines. I. Synthesis of Quino[1,2-*c*]quinazolinium Derivatives and the Related Indazolo[2,3-*a*]quinoline Derivatives as Analogs of the Antitumor Benzo[*c*]phenanthridine Alkaloids

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9,10-Dimethoxy-1,2,3,4,12,13-hexahydro-1-oxoquino[1,2-*c*]quinazolinium perchlorate, 1,2,3,4,13,24-hexahydro-1-oxo[1,3]dioxolo[4,5-*g*]quino[1,2-*c*]quinazolinium perchlorate, 6-methyl-2,3,9,10-tetramethoxyquino[1,2-*c*]quinazolinium perchlorate and 2,3-dimethoxy-13-methyl[1,3]dioxolo[4',5':6,7]quino[1,2-*c*]quinazolinium perchlorate were synthesized as analogs of the potent antitumor benzo[*c*]phenanthridine alkaloids nitidine and fagaronine. The related 2,3,8,9-tetramethoxyindazolo[2,3-*a*]quinoline and 2,3-dimethoxy[1,3]dioxolo[4,5-*g*]indazolo[2,3-*a*]quinoline were also synthesized. Further, the novel formation of 6,7-dimethoxy-2-(2-ethylamino-4,5-dimethoxyphenyl)quinoline *via* reductive alkylation with Raney nickel in refluxing ethanol is also reported.

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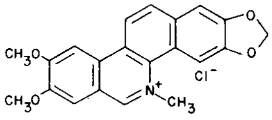
The benzo[*c*]phenanthridine alkaloids nitidine (**1**) (1,2) and fagaronine (**2**) (3) are known to possess potent antitumor activity against L1210 and P388 leukemias in mice (3-8). In addition, fagaronine has been shown to inhibit RNA directed DNA polymerase activity in avian myeloblastosis virus, Rauscher leukemia virus and simian sarcoma virus (9). Both alkaloids were later shown to be strong inhibitors of viral reverse transcriptase and DNA polymerase activities in NIH-Swiss mouse embryos (10). Further, it has been suggested that the mechanism of enzyme inhibition in both cases involves interaction with the adenine-thymine base pairs of the template primer (9,10). Recently, interest in nitidine has decreased due to the erratic toxicity it has shown in clinical trials (8,11). However, fagaronine is currently still in the process of development.

Several studies have appeared in the literature concerning the structure-activity relationships of various synthetic substituted benzo[*c*]phenanthridines (12-15) and of the relationship of these antitumor agents with related polycyclic hydrocarbons (16). However, these studies have not lead to the development of more potent and less toxic antitumor agents related to nitidine and fagaronine.

Notwithstanding this interest in the synthesis of structural isomers of nitidine and fagaronine, no study concerning the synthesis of aza analogs of these alkaloids has appeared in the literature. Because of this fact and due to the antitumor activity of coralyne (**3**), a berbinium alkaloid related to the benzo[*c*]phenanthridines (17-20), which contains a quaternized bridgehead nitrogen atom, the synthesis of quino[1,2-*c*]quinazolinium (**4**) derivatives was undertaken. This ring system is flat and contains a quaternized ring nitrogen atom, which are features known to be important in the biological activity of the benzo[*c*]phenanthridines (14,15).



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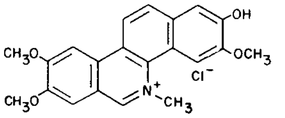

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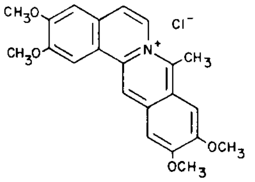

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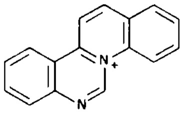

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A search of the literature revealed that the only quino[1,2-*c*]quinazoline which has been synthesized was reported by Jones in 1964 (21). He synthesized 1,2,3,4,12,13-hexahydro-9-methoxy-1-oxo-11b*H*-quino[1,2-*c*]quinazoline dihydrate as an aza steroid. The fully aromatic quino[1,2-*c*]quinazolinium ring system has not been reported in the literature.

Three synthetic routes were attempted in the synthesis of quino[1,2-*c*]quinazolines, two of which proved successful. The first of these routes is a modification of the procedure used by Jones (21) and is shown in Scheme I.

The starting 2-nitro-4,5-dimethoxyacetophenone (**5a**), 2-nitro-4,5-methylenedioxyacetophenone (**5b**) and 2-nitro-3,4,5-trimethoxyacetophenone (**5c**) were prepared by known procedures (21-24) and are all reported in the literature (24-26). Catalytic reduction of **5a-c** over palladium on carbon at room temperature and atmospheric pressure followed by formylation of the crude amino compounds with acetic formic anhydride gave the formamides **6a-c**. In the case of **6c**, low yields of the desired product made it impossible to continue this compound in the reaction sequence. Compounds **6a,b** were

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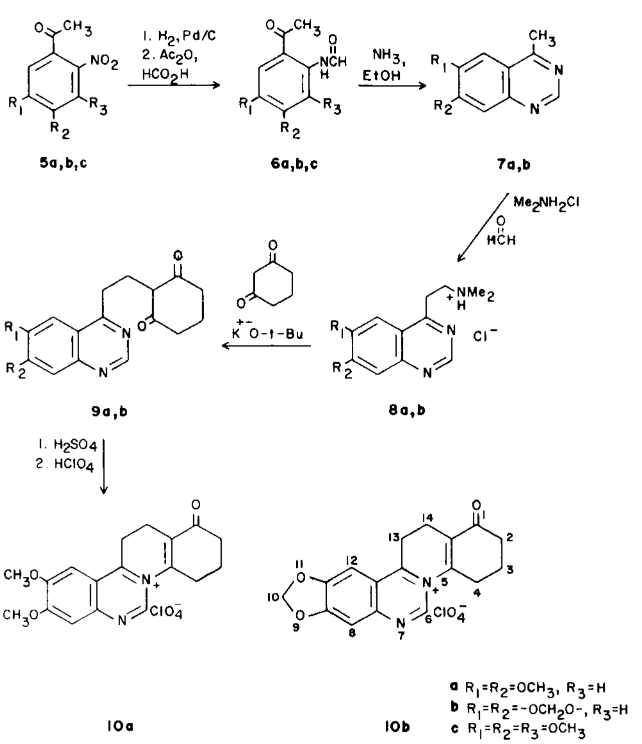
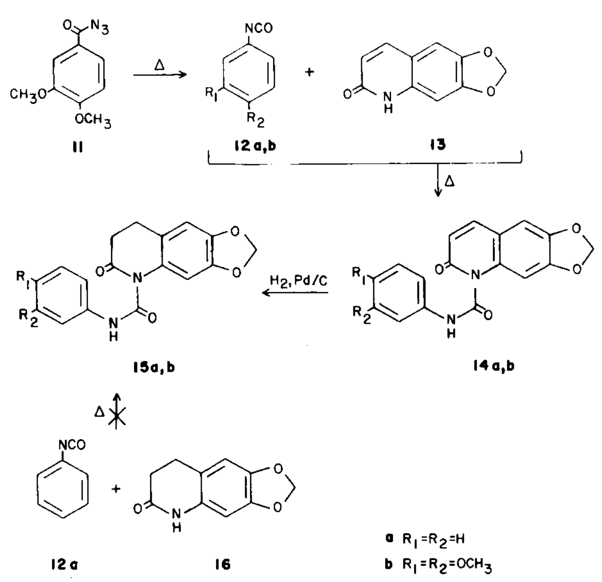
Scheme I



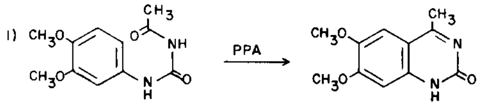
Scheme II



then reacted in a Bischler type quinazoline synthesis in a stainless steel bomb with ethanolic ammonia giving **7a,b**, which underwent Mannich reactions with dimethylammonium chloride and formaldehyde to give the Mannich bases **8a,b**. These were condensed with 1,3-cyclohexanedione in *t*-butyl alcohol in the presence of potassium *t*-butoxide giving **9a,b**, which were cyclized in concentrated sulfuric acid and precipitated as the perchlorate salts **10a,b**. This type of cyclization has been used by several groups in the synthesis of compounds containing a quaternized bridgehead nitrogen atom (27-29). The novel ring system of **10b** is shown with the correct orientation and systematic numbering.

Due to the length of this synthetic sequence from readily available starting materials and due to its limited versatility, the alternate synthesis outlined in Scheme II was attempted. In this sequence, **11** (30) was reacted with the carbostyrils **13** (31) in refluxing toluene giving **14b** *via* the isocyanate intermediate **12b**; in the case of **14a**, the reaction was carried out with the phenylisocyanate (**12a**) directly. Catalytic reduction of **14a,b** with palladium on carbon at room temperature and atmospheric pressure gave **15a,b**; **15a** could not be prepared directly by the condensation of **12a** with **16**.

All attempts to cyclize **14a,b** and **15a,b** to the desired quino[1,2-*c*]quinazolines under Bischler-Napieralski conditions in a variety of reagents (polyphosphoric acid, phosphorus oxychloride, phosphorus pentachloride and phosphorus pentoxide) proved unsuccessful. Only the starting materials or the cleaved carbostyril derivatives could be isolated from the reaction mixtures. This type of reaction was successful in the analagous example shown in equation 1 (32). However, due to the tertiary ring nitrogen atom in quinoline, **14a,b** and **15a,b** are unable to form imidoyl chloride and nitrilium chloride intermediates, which have recently been proposed to occur in Bischler-Napieralski type reactions (33). This fact could explain the difficulty with this synthetic route.

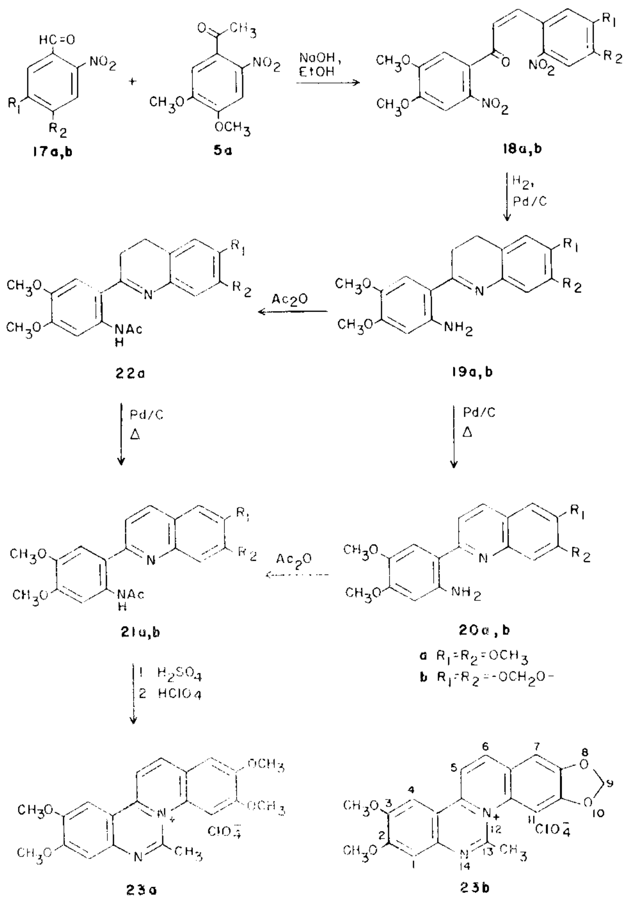


Equation 1

Finally, the synthesis of 6-methyl-2,3,9,10-tetramethoxyquino[1,2-*c*]quinazolinium perchlorate (**23a**) and 2,3-dimethoxy-13-methyl[1,3]dioxolo[4′,5′:6,7]quino[1,2-*c*]quinazolinium perchlorate (**23b**) was undertaken. These particular compounds were chosen because of the antitumor activity exhibited by nitidine (1) and the tetramethoxy analog of nitidine (13,14).

The synthesis of **23a** and **23b** proceed *via* the intermediate **21a,b** as shown in Scheme III. The starting 4,5-dimethoxy-2-nitrobenzaldehyde (**17a**), 4,5-methylenedioxy-2-nitrobenzaldehyde (**17b**) and 4,5-dimethoxy-2-nitroacetophenone (**5a**) were obtained by nitration of the readily available veratraldehyde, piperonal and 3,4-dimethoxyacetophenone, respectively, by known literature procedures (24,34,35). The base catalyzed aldol condensation of **17a,b** with **5a** in ethanol gave the dinitro compounds **18a,b**. Similar condensations have recently been performed by Rao, *et al.*, with pyridine derivatives in the preparation of streptonigrin related compounds (36). Catalytic reduction of **18a,b** over palladium on carbon in dimethylformamide at room temperature and atmospheric pressure gave the dihydroquinolines **19a,b**. These compounds were also obtained by catalytic hydrogenation in ethanol over palladium on carbon. However, ethanol proved to be an inferior solvent for this reaction due to the lack of solubility of the products and reactants, and due to the formation of a small amount of **20a,b** in the reaction mixture. Compounds **20a,b** were presumably formed during the work up when the ethanol-palladium on carbon solution was heated to boiling before filtration of the catalyst, giving catalytic dehydrogenation, thus necessitating a chromatographic separation of the products. Compounds **19a,b** were catalytically dehydrogenated with palladium on carbon in refluxing *p*-cymene to afford the fully aromatic quinolines **20a,b**. The formation of the acetamides **21a,b** was accomplished in refluxing acetic anhydride. The tetramethoxy analog **21a** was also formed by first acetylation and then aromatization starting with the dihydroquinoline **19a**, through the intermediate **22a**. However, this route gave a lower overall yield of the desired intermediate **21a**.

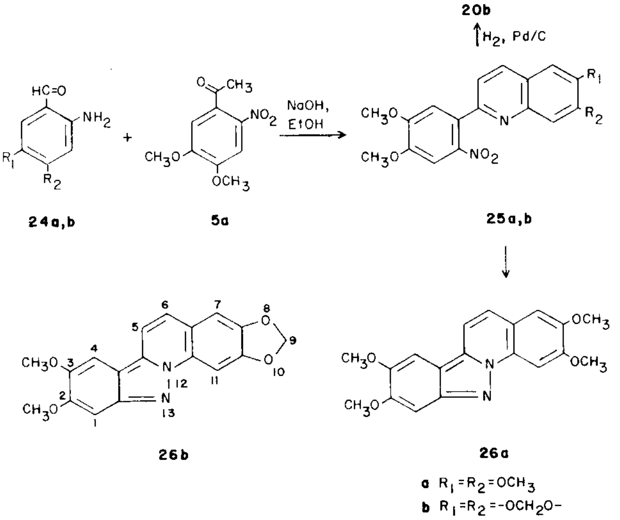
Scheme III



The cyclization of **21a,b** was again carried out in concentrated sulfuric acid followed by treatment of the crude products with perchloric acid to precipitate the desired perchlorate salts **23a,b**. The novel ring system of **23b** is shown with systematic numbering.

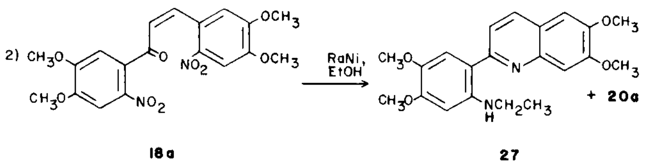
Due to the similarity of the indazolo[2,3-*a*]quinoline ring system with the quino[1,2-*c*]quinazolinium ring system, the synthesis of 2,3,8,9-tetramethoxyindazolo[2,3-*a*]quinoline (**26a**) and 2,3-dimethoxy[1,3]dioxolo[4,5-*g*]indazolo[2,3-*a*]quinoline (**26b**) was desired. Only a few indazolo[2,3-*a*]quinolines are reported in the literature, including the fully aromatic unsubstituted parent ring (37-39). Compounds **26a,b** were synthesized as shown in Scheme IV.

Scheme IV



The starting 2-amino-4,5-dimethoxybenzaldehyde (**24a**) (40) and 2-amino-4,5-methylenedioxybenzaldehyde (**24b**) (41) were synthesized by catalytic reduction of **5a** and **5b**, respectively, and were used without purification in a base catalyzed aldol condensation with **5a** to give the intermediates **25a** and **25b**, respectively. The desired products **26a,b** were obtained by reaction of **25a,b** with triethyl phosphite. Further, catalytic reduction of **25b** over palladium on carbon in dimethylformamide led to the amino compound **20b**.

The unusual formation of 6,7-dimethoxy-2-(2-ethylamino-4,5-dimethoxyphenyl)quinoline (**27**) was encountered in the attempted reduction of **18a** with Raney nickel in refluxing ethanol as shown in equation 2. In this reaction, a small amount of **20a** was also formed as a minor product; these products were separated by column chromatography. The structure of **27** was confirmed by spectral and analytical data.



Equation 2

Further research concerning the synthesis of benzo[*c*]phenanthridine alkaloid analogs is currently in progress in our laboratory.

EXPERIMENTAL

Ir spectra were obtained in potassium bromide discs on a Perkin Elmer model 457 spectrophotometer and a Beckman Acculab 2 spectrophotometer. ^1H Nmr spectra were obtained on a Varian EM 390 spectrometer and a JEOL FX 90 Q spectrometer in the solvents as indicated. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Mass spectra were obtained on a Hewlett-Packard model 5980A mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The following compounds were used as starting materials and were obtained from the Aldrich Chemical Company: veratraldehyde, veratric acid, piperonal, piperonylic acid, phenylisocyanate and 3,4-dimethoxyacetophenone.

2-Formamido-3,4,5-trimethoxyacetophenone (**6c**).

Compound **5c** (2.55 g., 0.01 mole) was hydrogenated at room temperature and atmospheric pressure in 80 ml. of ethanol over 0.25 g. of 10% palladium on carbon. After *ca.* 3 equivalents of hydrogen gas had been taken up by the reaction mixture, the catalyst was filtered and the solvent evaporated *in vacuo* giving the crude free amine as a yellow oil. This oil was slowly added to a solution of acetic formic anhydride, prepared according to the literature (42), while stirring in an ice bath. The mixture was then stirred overnight at room temperature and the excess solvent was removed *in vacuo*. The resulting green oily residue was neutralized with 10% sodium carbonate and extracted with chloroform. The resulting green solution was dried (sodium sulfate) and evaporation of the solvent gave a residue which was recrystallized in ethanol yielding 0.15 g. (6%) of yellow needles, m.p. 97-99°; ir: 3300-3100 (NH), 1640 (C=O); nmr (deuteriochloroform): 2.59 (s, CH_3, 3H), 3.86, 3.92 and 4.0 (3 singlets, OCH_3, 12H), 7.13 (s, phenyl, 1H), 8.73 (d, NHC*H*=O, 1H, J = 9 Hz), 9.4-9.8 (broad s, NH, 1H); ms: m/e 253 (M^+, 9.7), 210 (M-43, 100).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.12; H, 5.94; N, 5.33.

2-Formamido-4,5-dimethoxyacetophenone (**6a**) and 2-formamido-4,5-methylenedioxyacetophenone (**6b**) were prepared in an analagous manner in 62 and 73% yields, respectively, and are reported in the literature (24).

8-Methyl[1,3]dioxolo[4,5-*g*]quinazoline (**7b**).

A mixture of 6.7 g. (0.032 mole) of **6b** in 65 ml.of saturated ethanolic ammonia (saturated at −5°) was heated for 17 hours in a stainless steel bomb at 140°. Upon cooling, the solvent was removed *in vacuo* giving a crude tan precipitate which was recrystallized from ethanol giving 4.1 g. (68%) of white needles, m.p. 166-167°; ir: 1615, 1555, 1485 (quinazoline III, II and I bands, respectively); nmr (deuteriochloroform): 2.82 (s, CH_3, 3H), 6.15 (s, OCH_2O, 2H), 7.29 (s, H-4 and H-9, 2H), 9.05 (s, H-6, 1H); ms: m/e 188 (M^+, 100).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 64.16; H, 4.05; N, 15.16.

4-Methyl-6,7-dimethoxyquinazoline (**7a**).

The quinazoline **7a** was synthesized from **6b** in 82% yield as in the preparation of **7b**, m.p. 151-152°, lit. (24) m.p. 150-152°.

6,7-Dimethoxy-4-(*N*,*N*-dimethylaminoethyl)quinazoline Hydrochloride (**8a**).

A mixture of 2.0 g. (9.8 mmoles) of **7a**, 1.2 g. (14.7 mmoles) of dimethylamine hydrochloride, 1.0 ml. of 37% formaldehyde and 17 ml. of ethanol was warmed until all of the quinazoline dissolved. The orange solution was then allowed to stand in the dark for 22 hours, after which time the solvents were removed *in vacuo*. The light yellow product (1.85 g., 64%) which remained was dried and was used without further purification, m.p. 169-171°; ir: 1618, 1580, 1505 (quinazoline III, II and I bands, respectively), 1245, 1025 (C-O-CH_3); nmr (DMSO-d_6): 2.88 (s, $N(CH_3)_2$, 6H), 3.53-3.83 (m, -CH_2-CH_2-, 4H), 4.02 (s, OCH_3, 6H), 7.32 (s, H-8, 1H), 7.53 (s, H-5, 1H), 8.95 (s, H-2, 1H).

Anal. Calcd. for $C_{14}H_{20}ClN_3O_2$: C, 56.47; H, 6.77; N, 14.11. Found: C, 56.64; H, 6.88; N, 14.01.

8-(*N*,*N*-Dimethylaminoethyl)[1,3]dioxolo[4,5-*g*]quinazoline Hydrochloride (**8b**).

The quinazoline **8b** was synthesized from **7b** in a manner similar to the preparation of **8a**, and was isolated as a light tan powder in 80% yield, m.p. 218-220°; ir: 1610, 1560, 1490 (quinazoline III, II and I bands); nmr (trifluoroacetic acid): 3.21 and 3.29 (2 singlets, $N(CH_3)_2$, 6H), 4.08 (s, -CH_2-CH_2-, 4H), 6.5 (s, OCH_2O, 2H), 7.63 (s, H-4, 1H), 7.7 (s, H-9, 1H), 9.45 (s, H-6, 1H).

Anal. Calcd. for $C_{13}H_{16}ClN_3O_2$: C, 55.42; H, 5.72; N, 14.91. Found: C, 55.68; H, 5.69; N, 14.97.

4-[(1,3-Dioxocyclohex-2-yl)ethyl]-6,7-dimethoxyquinazoline (**9a**).

A mixture of 2.0 g. (6.72 mmoles) of **8a**, 36 ml. of *t*-butyl alcohol, 0.94 g. of potassium *t*-butoxide and 0.8 g. (7.14 mmoles) of 1,3-cyclohexanedione was refluxed for 43 hours under an atmosphere of nitrogen. The cloudy yellow solution was then filtered and the resulting tan precipitate was washed with hot chloroform. The solvents were removed *in vacuo* and the resulting crude product was recrystallized from ethanol giving 0.8 g. (36%) of fine white needles, m.p. 238° dec.; ir: 1620 (C=O), 1275, 1020 (C-O-CH_3); nmr (DMSO-d_6): 1.67-1.92 [m, CH_2 (5-cyclohexyl), 2H], 2.9-3.2 [m, CH_2 (4- and 6-cyclohexyl), 4H], 3.32-3.77 (m, -CH_2-CH_2-, 4H), 3.95 and 3.99 (2 singlets, OCH_3, 6H), 7.25 (s, H-8, 1H), 7.73 (s, H-5, 1H), 8.9 (s, H-2, 1H); ms: m/e 328 (M^+, 3.4), 204 (100).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.69; H, 6.14; N, 8.34.

As in the case of 2-acetyl-1,3-cyclohexanedione (43), the H-2 proton in the cyclohexyl group is unobserved in the nmr due to the tautomerization of cyclohexanedione.

8-[1,3-Dioxocyclohex-2-yl)ethyl][1,3]dioxolo[4,5-*g*]quinoline (**9b**).

Compound **9b** was synthesized from **8b** in a manner similar to the preparation of **9a**, and was obtained as fine white needles in 45% yield, m.p. 220-221°; ir: 1630 (C=O); nmr (deuteriochloroform): 1.8-2.13 [m, CH_2 (5-cyclohexyl), 2H], 2.22-2.6 [m, CH_2 (4- and 6-cyclohexyl), 4H], 2.92 (t, quinazoline-CH_2-C*H*$_2$-, 2H, J = 4 Hz), 3.5 (t, quinazoline-C*H*$_2$-CH_2-, 2H), 6.22 (s, OCH_2O, 2H), 7.3 (s, H-4, 1H), 7.33 (s, H-9, 1H), 9.03 (s, H-6, 1H), as in the case of **9a**, the H-2 proton in the cyclohexyl group is unobserved; ms/ m/e 312 (M^+, 3.1), 187 (M-125, 100).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.36; H, 5.13; N, 8.90.

9,10-Dimethoxy-1,2,3,4,12,13-hexahydro-1-oxoquino[1,2-*c*]quinazolinium Perchlorate (**10a**).

A mixture of 0.35 g. (1.07 mmoles) of **9a** in 9 ml. of concentrated sulfuric acid was gently warmed until all of the solid had dissolved. The mixture was allowed to stand for 10 hours, after which time the mixture was cautiously poured into 120 ml. of anhydrous ether and allowed to stand in the refrigerator overnight, giving a white gummy residue. The residue was treated with decolorizing carbon in water. The mixture was then filtered into 8 ml. of 35% perchloric acid giving white needles, which were filtered and dried (0.35 g., 80%), m.p. 196-198°; ir: 1640 (C=O); nmr (deuteriochloroform): 1.7-2.1 (m, H-3, 2H), 2.25-2.5 (m, H-2 and H-4, 4H), 2.65-2.98 (m, H-13, 2H), 3.3-3.6 (m, H-12, 2H), 4.2 (s, OCH_3, 6H), 7.7 (s, H-8, 1H), 7.95 (s, H-11, 1H), 9.28 (s, H-6, 1H) (44).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_7 \cdot H_2O$: C, 50.42; H, 4.94; N, 6.53. Found: C, 50.70; H, 4.90; N, 6.18.

1,2,3,4,13,14-Hexahydro-1-oxo[1,3]dioxolo[4,5-*g*]quino[1,2-*c*]quinazolinium Perchlorate (**10b**).

This compound was prepared from **9b** in a manner similar to the synthesis of **10a**, and was obtained as fine white needles in 87% yield, m.p. 226-229°; ir: 1645 (C=O); nmr (DMSO-d_6): 1.7-2.0 (m, H-3, 2H), 2.2-2.4 (m, H-2 and H-4, 4H), 2.6-2.8 (m, H-14, 2H), 3.25-3.45 (m, H-13, 2H), 6.57 (s, OCH_2, 2H), 7.7 (s, H-8, 1H), 8.0 (s, H-12, 1H), 6.27 (s, H-6, 1H) (44).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_7 \cdot 1.4\,H_2O$: C, 48.62; H, 4.27; N, 6.67. Found: C, 49.05; H, 4.41; N, 6.17.

5-Anilinocarbonyl[1,3]dioxolo[4,5-*g*]quinolin-6-(5*H*)one (**14a**).

A mixture of 5.0 g. (0.0264 mole) of the starting carbostyril **13** (31) and 3.15 g. (0.0264 mole) of phenylisocyanate (**12a**) in 200 ml. of toluene was refluxed for 9 hours. The cloudy mixture was then cooled and filtered, and the resulting tan precipitate was washed with toluene and dried. This compound was not further purified (7.70 g., 95%), m.p. 244-245°; ir: 3600 (NH), 1695 (C=O); nmr (DMSO-d_6): 6.02 (s, OCH_2O, 2H), 6.35 (d, H-8, 1H, $J_{7,8}$ = 18 Hz), 6.8-7.05 (broad s, NH, 1H), 7.2-7.5 (m, phenyl, 5H), 7.78 (d, H-7, 1H), 8.45 (s, H-9, 1H), 8.95 (s, H-4, 1H); ms: m/e 308 (M^+, 5.2), 189 (M-phenylisocyanate, 100 (44).

Anal. Calcd. for $C_{17}H_{12}N_2O_4 \cdot 0.75\,H_2O$: C, 63.45; H, 4.23; N, 8.70. Found: C, 63.57; H, 4.27; N, 8.59.

5-(3,4-Dimethoxyanilino)carbonyl[1,3]dioxolo[4,5-*g*]quinolin-6-(5*H*)one (**14b**).

A mixture of 5.0 g. (0.0264 mole) of the starting carbostyril **13** (31) and 5.47 g. (0.0264 mole) of 3,4-dimethoxybenzoyl azide (**11**) (30) was refluxed in 220 ml. of dry toluene for 14 hours. The mixture was then cooled, filtered, and the resulting tan precipitate was washed with toluene and dried giving 9.05 g. (93%) of light tan powder, m.p. 251° dec.; ir: 3600 (NH), 1690 (C=O); nmr (DMSO-d_6): 3.71 and 3.73 (2 singlets, OCH_3, 6H), 6.07 (s, OCH_2O, 2H), 6.4 (d, H-7, 1H, $J_{7,8}$ = 17 Hz), 6.9 (s, NH, 1H), 7.22, 7.25 and 7.37 (3 singlets, phenyl 3H), 7.78 (d, H-8, 1H), 8.35 (s, 9-H, 1H), 8.8 (s, 4H, 1H) (44).

Anal. Calcd. for $C_{19}H_{16}N_2O_5 \cdot 0.6\,H_2O$: C, 60.19; H, 4.57; N, 7.39. Found: C, 60.06; H, 4.68; N, 7.06.

5-Anilinocarbonyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]quinolin-6-(5*H*)one (**15a**).

A mixture of 2.0 g. (6.49 mmoles) of **14a** in 80 ml. of glacial acetic acid was hydrogenated over 0.5 g. of 10% palladium on carbon. The reaction was stopped after *ca.* 2 equivalents of hydrogen gas were taken up by the reaction mixture. The mixture was then warmed until all of the product dissolved and the catalyst was filtered. On cooling, a white precipitate formed which was filtered and recrystallized in ethanol giving 1.2 g. (60%) of white needles, m.p. 216°; ir: 3500 (NH), 1710 (C=O); nmr (DMSO-d_6): 2.4-2.6 (m, H-8, 2H), 2.65-2.85 (m, H-7, 2H), 5.99 (s, OCH_2O, 2H), 6.95-7.1 (m, NH, 1H), 7.2-7.6 (m, phenyl, 5H), 7.85 (s, H-9, 1H), 8.9 (s, H-4, 1H); ms: m/e 69 (phenylisocyanate, 100) (44).

Anal. Calcd. for $C_{17}H_{14}N_2O_4 \cdot H_2O$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.32; H, 4.79; N, 8.57.

5-(3,4-Dimethoxyanilino)carbonyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]quinolin-6-(5*H*)one (**15b**).

Compound **15b** was prepared from **14b** in a similar manner to the synthesis of **15a**, and was obtained as a white powder in 71% yield, m.p. 221° dec.; ir: 3060 (NH), 1690 (C=O); nmr (DMSO-d_6): 2.4-2.5 (m, H-8, 2H), 2.6-2.8 (m, H-7, 2H), 3.71 and 3.72 (2 singlets, OCH_3, 6H), 5.95 (s, OCH_2O, 2H), 6.8 and 7.2 (2 singlets, phenyl, 3H), 6.86 (s, NH, 1H), 7.8 (s, H-4, 1H), 8.72 (s, H-9, 1H) (44).

Anal. Calcd. for $C_{19}H_{18}N_2O_6 \cdot H_2O$: C, 58.76; H, 5.19; N, 7.21. Found: C, 59.06; H, 5.21; N, 6.96.

1-(4,5-Dimethoxy-2-nitrophenyl)-3-(4,5-dimethoxy-2-nitrophenyl)-2-propen-1-one (**18a**).

A mixture of 32.0 g.(0.142 mole) of **17a** (34) and 30.0 g. (0.142 mole) of **5a** (24) was suspended in 1400 ml. of ethanol. The mixture was then stirred in an ice bath while a solution of 14 g. of sodium hydroxide dissolved in 55 ml. of water was slowly added dropwise. After stirring in the ice bath for 0.5 hour and then at room temperature for 4 hours, the suspension, which had become deep red in color, was filtered and the resulting yellow precipitate was washed with ethanol. Following recrystallization in dimethylformamide, 33.4 g. (56%) of small yellow plates were isolated, m.p. 216-217° dec.; ir: 1515, 1335 (NO_2), 1270, 1065 (C-O-CH_3); nmr (DMSO-d_6): 3.9-4.0 (m, OCH_3, 12H), 7.2 (s, phenyl, 1H), 7.27 (d, =C*H*-C=O, 1H, J = 16 Hz), 7.42, 7.67 (2 singlets, phenyl, 2H), 7.73 (d, =CH-phenyl, 1H), 7.78 (s, phenyl, 1H); ms: m/e 311 (7.9), 140 (100).

Anal. Calcd. for $C_{19}H_{18}N_2O_9$: C, 54.55; H, 4.34; N, 6.70. Found: C, 54.73; H, 4.29; N, 6.53.

1-(4,5-Dimethoxy-2-nitrophenyl)-3-(4,5-methylenedioxy-2-nitrophenyl)-2-propen-1-one (**18b**).

Compound **18b** was prepared from **17b** and **5a** in a manner similar to the preparation of **18a**, and was obtained as light yellow needles in 25% yield, m.p. 252-253° dec.; ir: 1660 (C=O), 1510, 1320 (NO_2), 1220, 1035 (C-OCH_3); nmr (DMSO-d_6): 3.1 (s, OCH_3, 6H), 6.3 (s, OCH_2O, 2H), 7.0 (d, =CH-C=O, 1H, J = 12.5 Hz), 7.2 and 7.55 (2 singlets, aromatic, 2H), 7.57 (d, =CH-phenyl, 1H), 7.61 and 7.71 (2 singlets, aromatic, 2H); ms: m/e 357 (22.5), 356 (100).

Anal. Calcd. for $C_{18}H_{14}N_2O_9$: C, 53.74; H, 3.51; N, 6.96. Found: C, 53.54; H, 3.53; N, 6.76.

2-(2-Amino-4,5-dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxyquinoline (**19a**).

Compound **18a** (14.5 g., 0.0347 mole) was hydrogenated at room temperature and atmospheric pressure in 380 ml. of dimethylformamide over 2.0 g. of 5% palladium on carbon. After the mixture had taken up *ca.* 7 equivalents of hydrogen, the reaction was stopped and the catalyst was filtered giving a yellow-green solution. Removal of the solvent *in vacuo* gave a yellow-green residue, which was crystallized in ethanol giving 7.0 g. of yellow plates (59%), m.p. 206°; ir: 3440, 3210 (NH_2); nmr (DMSO-d_6): 2.76 (s, -CH_2-CH_2-, 4H), 3.74-3.8 (m, OCH_3, 12H), 6.4, 6.8, 6.88 and 7.13 (4 singlets, aromatic, 4H), 7.53 (s, NH_2, 2H); ms: m/e 342 (M^+, 100).

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.82; H, 6.45; N, 7.96.

2-(2-Amino-4,5-dimethoxyphenyl)-7,8-dihydro[1,3]dioxolo[4,5-*g*]quinoline (**19b**).

Compound **19b** was synthesized from **18b** in a manner similar to the preparation of **19a**, and was obtained as small yellow needles in 62% yield, m.p. 220-222°; ir: 3440, 3220 (NH_2); nmr (DMSO-d_6): 2.7 (s, -CH_2-CH_2-, 4H), 3.7, 3.78 (2 singlets, OCH_3, 3H), 5.92 (s, OCH_2O, 2H), 6.35, 6.72, 6.78 and 7.08 (4 singlets, aromatic, 4H); ms: m/e 326 (M^+, 100).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.57; H, 5.53; N, 8.35.

2-(2-Amino-4,5-dimethoxyphenyl)-6,7-dimethoxyquinoline (**20a**).

Compound **19a** (3.0 g., 8.76 mmoles) and 0.8 g. of 5% palladium on carbon were refluxed in 250 ml. of *p*-cymene for 36 hours under an atmosphere of nitrogen. The catalyst was then filtered from the hot solution and yellow plates were formed on cooling. These crystals were triturated in hot ethanol giving 2.2 g. (74%) of **20a**, m.p. 245-247°; ir: 3460, 3280 (NH_2); nmr (DMSO-d_6): 3.77, 3.92 and 3.98 (3 singlets, OCH_3, 12H), 6.48 (s, aromatic, 1H), 6.89 (s, NH_2, 2H), 7.28 and 7.33 (2 singlets, aromatic, 3H), 7.77 (d, H-3, 1H, $J_{3,4}$ = 9 Hz), 8.12 (d, H-4, 1H); ms: m/e 340 (M^+, 76.2), 325 (M-CH_3, 100).

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.30; H, 5.97; N, 7.97.

2-(2-Amino-4,5-dimethoxyphenyl)[1,3]dioxolo[4,5-*g*]quinoline (**20b**).

Method A.

Compound **20b** was synthesized from **19b** in a manner similar to the preparation of **20a**, and was obtained as yellow plates in 75% yield, m.p. 212-214°; ir: 3450, 3290 (NH_2); nmr (deuteriochloroform): 3.9 (s, OCH_3, 6H), 5.7-6.1 (broad s, NH_2, 2H), 6.07 (s, OCH_2O, 2H), 6.32, 7.02, 7.18 and 7.28 (4 singlets, aromatic 4H), 7.57 (d, H-3, 1H, $J_{3,4}$ = 9 Hz), 7.97 (d, H-4, 1H); ms: m/e 324 (M^+, 100).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.70; H, 4.79; N, 8.43.

Method B.

Compound **25b** (0.8 g., 2.26 mmoles) dissolved in 30 ml. of dimethylformamide was hydrogenated over 0.2 g. of 5% palladium on carbon at room temperature and atmospheric pressure, and the reaction was stopped after the uptake of *ca.* 3 equivalents of hydrogen gas. After the work up as in the preparation of **19a**, 0.50 g. (68%) of yellow plates were isolated having the same m.p. and spectral properties as **20b** prepared *via* Method A.

2-(2-Acetamido-4,5-dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxyquinoline (**22a**).

A mixture of 1.0 g. (2.92 mmoles) of **19a** and 20 ml. of acetic anhydride was refluxed for 0.5 hour, after which time the acetic anhydride was removed *in vacuo*. The crude yellow product which formed was passed through a column of silica gel using chloroform as an eluent. The product thus isolated (first product) was recrystallized in ethanol giving 0.3 g. of yellow plates, m.p. 179-180°; ir: 3600-3300 (NH), 1670 (C=O); nmr (deuteriochloroform): 2.3 (s, CH_3, 3H), 2.93 (s, $-CH_2-CH_2-$, 4H), 3.92-4.0 (m, OCH_3, 12H), 6.77, 6.93, 7.22 and 8.52 (4 singlets, aromatic, 4H), 13.67-13.82 (broad s, NH); ms: m/e 369 (M-15, 11), 341 (100).

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.30; N 7.29. Found: C, 66.11; H, 6.36; N, 7.06.

2-(2-Acetamido-4,5-dimethoxyphenyl)-6,7-dimethoxyquinoline (**21a**).

Method A.

A mixture of 0.75 g. (2.19 mmoles) of **20a** and 20 ml. of acetic anhydride was refluxed for 20 minutes. The solvent was then removed *in vacuo* and the resulting yellow residue was recrystallized in ethanol giving 0.7 g. (83%) of yellow crystals, m.p. 179°; ir: 3600-3300 (NH), 1680 (C=O); nmr (DMSO-d_6): 2.2 (s, CH_3, 3H), 3.89, 3.92, 4.0 and 4.02 (4 singlets, OCH_3, 12H), 7.38 and 7.48 (2 singlets, aromatic, 3H), 7.9 (d, H-3, 1H, $J_{3,4}$ = 9 Hz), 8.2 (s, aromatic, 1H), 8.3 (d, H-4, 1H), 12.8 (s, NH, 1H); ms: m/e 382 (M^+, 57.1), 367 ($M-CH_3$, 100).

Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 66.31; H, 6.36; N, 7.36. Found: C, 66.47; H, 6.00; N, 7.20.

Method B.

A mixture of 0.5 g. (1.31 mmoles) of **22a** and 0.3 g. of 5% palladium on carbon was refluxed in 30 ml. of *p*-cymene for 9 hours. The product was worked up as in the preparation of **20a** giving yellow crystals with the same m.p. and spectral data as the product prepared *via* Method A.

2-(2-Acetamido-4,5-dimethoxyphenyl)[1,3]dioxolo[4,5-*g*]quinoline (**21b**).

A mixture of 0.4 g. (1.23 mmoles) of **20b** in 20 ml. of acetic anhydride was refluxed for 0.5 hour, after which time the product was worked up as in the preparation of **21a** (Method A), giving 0.23 g. of yellow plates (51%), m.p. 222-224°; ir: 1665 (C=O); nmr (DMSO-d_6): 2.2 (s, CH_3, 3H), 3.82 and 3.89 (2 singlets, OCH_3, 6H), 6.25 (s, OCH_2O, 2H), 7.35-7.48 (m, H-4, H-9 and phenyl, 4H), 7.88 (d, H-7, 1H, $J_{7,8}$ = 9 Hz), 8.25 (d, H-8, 1H), 12.55 (s, NH, 1H); ms: m/e 366 (M^+, 61), 351 ($M-CH_3$, 100).

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.82; H, 4.86; N, 7.44.

2,3,9,10-Tetramethoxy-6-methylquino[1,2-*c*]quinazolinium Perchlorate (**23a**).

Compound **23a** was prepared from **22a** in a manner similar to the preparation of **10a**, and was obtained as yellow needles in 72% yield, m.p. 265-267° dec.; ir: 1660 (C=O), 1500, 1280 ($C-O-CH_3$); nmr (DMSO-d_6): 1.92 (s, CH_3, 3H), 3.88, 4.03, 4.08 (3 singlets, aromatic, 4H), 7.79 (d, H-12, 1H, $J_{12,13}$ = 9 Hz), 8.78 (d, H-13, 1H) (44).

Anal. Calcd. for $C_{21}H_{21}ClN_2O_8 \cdot 1.5 H_2O$: C, 50.27; H, 4.54; N, 5.86. Found: C, 50.50; H, 4.76; N, 5.43.

2,3-Dimethoxy-13-methyl[1,3]dioxolo[4',5':6,7]quino[1,2-*c*]quinazolinium Perchlorate (**23b**).

Compound **23b** was synthesized from **21b** in a manner similar to the preparation of **23a**, and was obtained as a yellow powder in 10% yield, m.p. 274-275° dec.; ir: 1660 (C=O); nmr (DMSO-d_6): 1.9 (s, CH_3, 3H), 3.5-3.9 (m under a water peak, OCH_3), 6.4 (s, OCH_2O, 2H), 7.46, 7.5 (2 singlets, aromatic, 2H), 7.7 (d, H-12, 1H, J = 9 Hz), 7.8 and 7.92 (2 singlets, aromatic, 2H), 7.9 (d, H-13, 1H) (44).

Anal. Calcd. for $C_{20}H_{17}ClN_2O_8 \cdot 2.5 H_2O$: C, 48.64; H, 4.49; N, 5.67. Found: C, 48.71; H, 4.42; N, 5.55.

6,7-Dimethoxy-2-(2-nitro-4,5-dimethoxyphenyl)quinoline (**25a**).

The amino compound **24a** was synthesized by catalytically hydrogenating 6 g. (0.0284 mole) of **17a** in 200 ml. of ethanol over 0.8 g. of 5% palladium on carbon at room temperature and atmospheric pressure. Following the uptake of *ca.* 3 equivalents of hydrogen gas, the mixture was filtered and the solvent was removed *in vacuo* giving a yellow-green oil (**24a**), which was used without purification in the next step. A mixture of the crude **24a** and 5.8 g. of the acetophenone **5a** in 200 ml. of ethanol was then stirred in an ice bath. To this mixture, 1.8 g. of sodium hydroxide dissolved in 10 ml. of water was slowly added dropwise. The resulting red-brown mixture was stirred overnight at room temperature and filtered, giving a yellow solid which was recrystallized in ethyl acetate. Thus, 2.0 g. (20% based on **24a**) of **25a** were isolated, m.p. 224-225°; ir: 1540, 1360 (NO_2); nmr (deuteriochloroform): 3.99 and 4.0 (2 singlets, OCH_3, 12H), 7.1 (s, aromatic, 2H), 7.29 (d, H-3, 1H, $J_{3,4}$ = 9 Hz), 7.45 and 7.6 (2 singlets, aromatic, 2H), 8.0 (d, H-4, 1H); ms: m/e 370 (M^+, 100).

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.50; H, 4.79; N, 7.38.

6-(2-Nitro-4,5-dimethoxyphenyl)[1,3]dioxolo[4,5-*g*]quinoline (**25b**).

This compound was synthesized from **24b** and **5a** in a manner similar to the preparation of **25a**, and was isolated as yellow needles in 19% yield, m.p. 204-205°; ir: 1510, 1370 (NO_2); nmr (DMSO-d_6): 3.97 (s, OCH_3, 6H), 6.23 (s, OCH_2O, 2H), 7.25 and 7.4 (2 singlets, aromatic, 3H), 7.57 (d, H-7, 1H, $J_{7,8}$ = 8 Hz), 7.63 (s, aromatic 1H), 8.25 (d, H-8, 1H); ms: m/e 354 (M^+, 17), 250 (M-104, 100).

Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 59.52; H, 4.00; N, 7.64.

2,3,8,9-Tetramethoxyindazolo[2,3-*a*]quinoline (**26a**).

A mixture of 0.55 g. (1.49 mmoles) of **26a** and 20 g. of triethyl phosphite was refluxed in 20 ml. of xylene for 48 hours. After completion of the reaction, the solvents were removed *in vacuo* giving a crude yellow product which was recrystallized in ethanol. The product was isolated as yellow needles (0.3 g., 60%); m.p. 217-218°; ir: 1220, 1020 ($C-OCH_3$); nmr (deuteriochloroform): 3.99, 4.0, 4.06 and 4.19 (4 singlets, OCH_3, 12H), 6.95, and 7.1 (2 singlets, aromatic 2H), 7.17 (d, H-5, 1H, $J_{5,6}$ = 9 Hz), 7.18 (s, aromatic, 1H), 7.45 (d, H-6, 1H), 8.06 (s, aromatic, 1H); ms: m/e 338 (M^+, 96), 323 ($M-CH_3$, 100).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.27; H, 5.23; N, 8.09.

2,3-Dimethoxy[1,3]dioxolo[4,5-*g*]indazolo[2,3-*a*]quinoline (**26b**).

Compound **26b** was synthesized from **25b** in a manner similar to the preparation of **26a**, and was obtained as yellow needles, m.p. 246-247°, in

58% yield; ir: 1020 (C-OCH_3); nmr (deuteriochloroform): 4.0 and 4.02 (2 singlets, OCH_3, 12H), 6.15 (s, OCH_2, 2H), 7.1 and 7.2 (2 singlets, aromatic 3H), 7.32 (d, H-5, 1H, $J_{5,6}$ = 10 Hz, 7.65 (d, H-6, 1H), 8.18 (s, aromatic, 1H); ms: m/e 322 (M^+, 100), 307 (M-CH_3, 91).

Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.10; H, 4.53; N, 8.81.

6,7-Dimethoxy-2-(2-ethylamino-4,5-dimethoxyphenyl)quinoline (**27**).

A mixture of 4.0 g. (9.56 mmoles) of **18a** and 40.0 g. of wet Raney nickel was refluxed in 600 ml. of ethanol for 2 hours, after which time the hot solution was filtered to remove the catalyst. On standing, the resulting yellow solution deposited yellow crystals, which were filtered. This product showed 2 spots on tlc (chloroform as eluent). Column chromatography over silica gel with chloroform as the eluent gave 0.5 g. of **27** (14%) as the first and major product (after recrystallization in ethanol), along with a small amount of **20a** (second product, 0.05 g., 1.4%, after recrystallization in ethanol). Compound **20a** was identical to the previously prepared **20a** with respect to m.p. and spectral properties. Compound **27** had m.p. 164° and was obtained as yellow needles; ir: 3020-4080 (NH), 1215, 1000 (C-OCH_3); nmr (DMSO-d_6): 1.38 (t, CH_2CH_3, 3H, J = 7 Hz), 3.32 (d, CH_2CH_3, 2H), 3.79, 3.85, 3.92 and 3.97 (4 singlets, OCH_3, 12H), 6.35, 7.27, 7.29 and 7.42 (4 singlets, aromatic, 4H), 7.84 (d, H-3, 1H, $J_{3,4}$ = 9 Hz), 8.17 (d, H-4, 1H); ms: m/e 368 (M^+, 97), 353 (M-CH_3, 100), 337 (M-2CH_3, 21).

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.73; H, 6.60; N, 7.36.

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(44) Repeated attempts to dry this compound *in vacuo* over phosphorus pentoxide did not result in complete dehydration.