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Synthesis and Structure–Activity Relationships of Heterocyclic Compounds Containing a Trimethoxyarene Function

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Pyrazole-, isoxazole-, and pyrazolone-containing systems were prepared from 3,4-dihydro-5,6,7-trimethoxy-1(2*H*)-naphthalenone, 3,4-dihydro-6,7,8-trimethoxy-1(2*H*)-naphthalenone, and 3,4-dihydro-6,7,8-trimethoxy-1(2*H*)-phenanthrone. Primarily, the pyrazoles displayed inhibition of growth in the microbial screens and in tissue culture. Correlation of the heteroatom distances between the oxygen atoms of two methoxy groups and a nitrogen atom in the pyrazole function with the percent plating efficiency on KB cell growth suggests increased inhibition as the $(O^A–N)/(O^B–N)$ ratio deviates from one. No trend was observed in relating the $O^A–N–O^B$ angle and activity for the examples studied.

A large number of polymethoxyarene-substituted compounds are known to be physiologically active.[1-3] A number of physiologically active azasteroids have been reported and several reviews on this subject have been written[4] but very few contain a polymethoxyarene group. As part of our continuing study of the activity of azasteroid systems[5] we selected for study pyrazoles, isoxazoles, and pyrazolones synthesized from 3,4-dihydro-5,6,7-trimethoxy-1(2*H*)-naphthalenone (**1a**),[5] 3,4-dihydro-6,7,8-trimethoxy-1(2*H*)-naphthalenone (**1b**),[6] and 3,4-dihydro-6,7,8-trimethoxy-1(2*H*)-phenanthrone (**2**). This paper reports the synthesis of these compounds and the correlation of heteroatom distances and plating efficiency of KB cells determined for the pyrazole analogs.

Chemistry. Phenanthrone **2** was synthesized from **1a** by initial condensation with methyl 4-bromocrotonate in a Reformatsky reaction. This was followed by dehydration and isomerization to form the naphthalene butyric ester **3** which was saponified in aqueous KOH. The resulting acid **4** was cyclized in the presence of polyphosphoric acid (PPA) to form **2** (Scheme I).

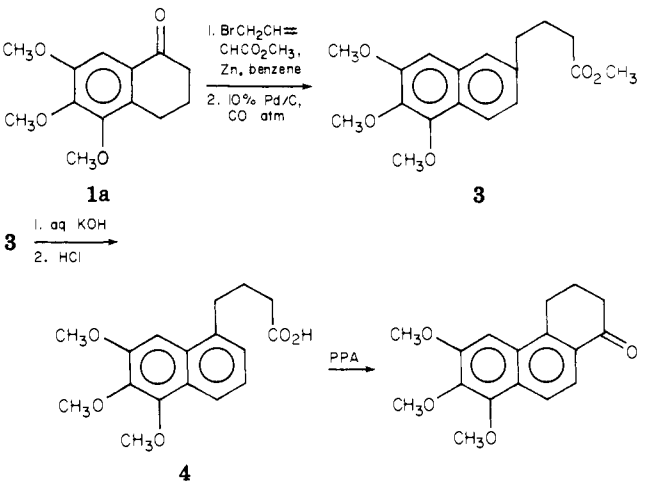
Treatment of **1a**, **1b**, or **2** with ethyl formate in the presence of $NaOCH_3$ gave the corresponding hydroxymethylene derivative **5a**, **5b**, or **6**. Pyrazole derivatives **7a**, **7b**, and **8** were obtained by treatment of the corresponding hydroxymethylene derivative with hydrazine in methanol (Schemes II and III).

The isoxazole derivatives **9a**, **9b**, and **10** were prepared[7] from the corresponding hydroxymethylene compounds for the formation of the [2,3-*d*] isomer. Formation of the α-keto ester **11a** from **1a** was successfully achieved by heating **1a** in anhydrous dimethyl carbonate while treatment of **11a** with hydrazine gave pyrazolone **12a** (Scheme IV).

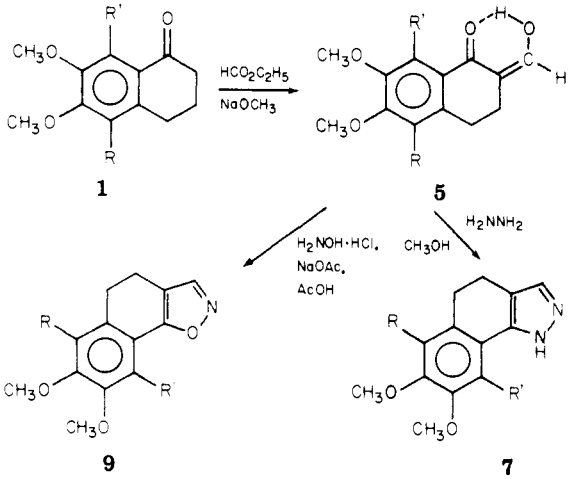
In one case the α-keto ester **11a** was not isolated but, in the presence of an additional equivalent of base, CH_3I in CH_3OH was added to form **11b**. Likewise, **11c** was prepared from the tetralone **1b** and **13** was prepared from the phenanthrone **2**. Treatment of **11a**, **11b**, or **13** with hydrazine in methanol yielded the corresponding pyrazolones **12a**, **12b**, and **14** (Scheme V).

Biological Results and Discussion. *Bacillus subtilis* W23 (a prototrophic strain) and *Pseudomonas fluorescens* NND were chosen for the microbial screening (Table I).

Scheme I

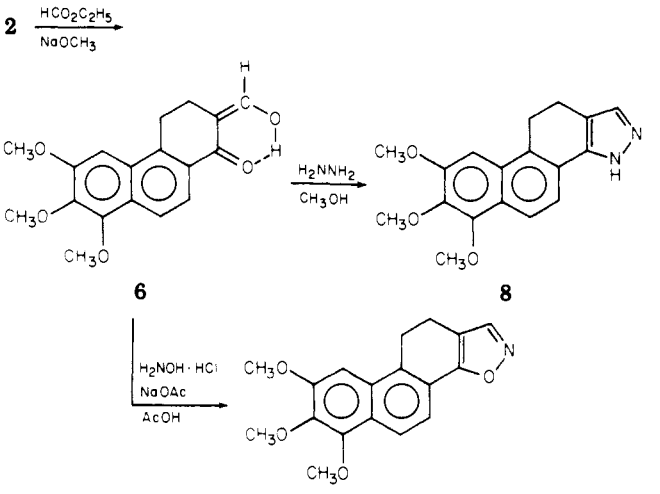


Scheme II

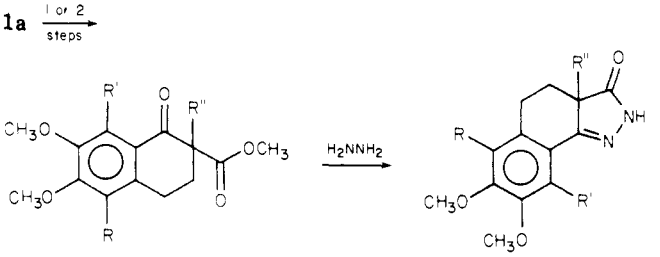


a, R = OCH_3; R′ = H
b, R = H; R′ = OCH_3

Scheme III



Scheme IV



a, R = OCH_3; R′ = H; R″ = H
b, R = OCH_3; R′ = H; R″ = CH_3
c, R = H; R′ = OCH_3; R″ = CH_3

Those compounds showing some activity (which, interestingly, were only the pyrazoles) were evaluated on their ability to inhibit the plating efficiency of the human tumor cell line KB.[8] Since pyrazoles **15** and **16** and the thiazole **17** were available in our laboratory[9] and are structurally related to the active pyrazoles in this study, they were included in the biological screening and structure–activity correlation studies. The results of the tissue culture screens are shown in Table II.

Zee-Cheng and Cheng[10,11] reported a possible correlation

Scheme V

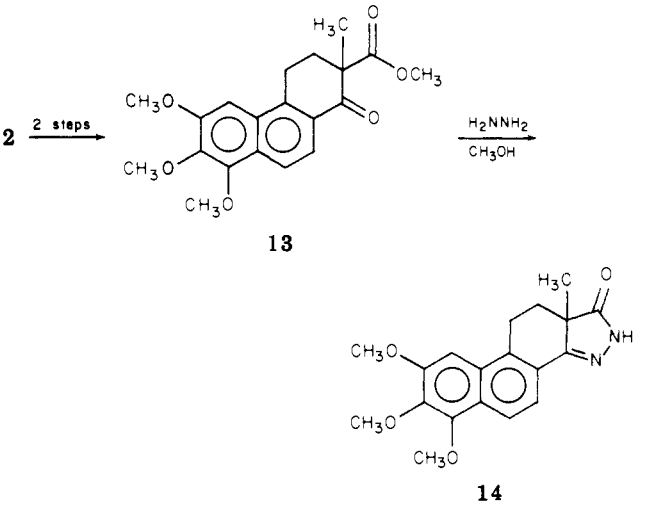
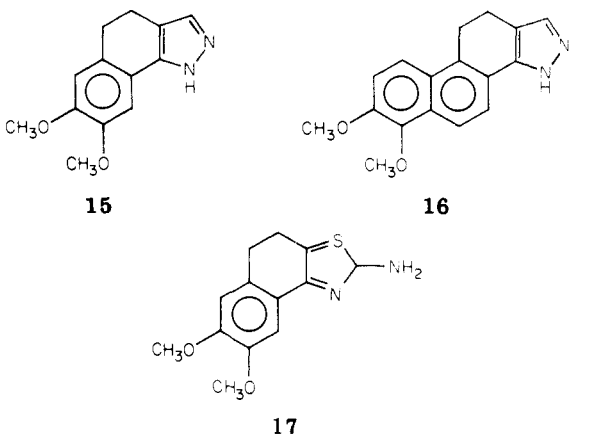


Table I. Activity of Products in Microbial Tests

Compd	*B. subtilis*[a]	*P. flourescens*	Compd	*B. subtilis*[a]	*P. flourescens*
7a	±[b]	–	**12a**	±[b]	–
7b	+	–	**12b**	–	–
8	+	–	**12c**	–	–
9a	–	–	**14**	–	–
9b	–	–	**15**	+	–
			16	+	–
10	–	–	**17**	+	–

[a] +, inhibition; –, no inhibition; ±, slight inhibition. All concentrations at ~91 μg/ml. Growth was measured after 14 hr of incubation at 37°. [b] 4-hr lag in growth followed by slower growth rate.

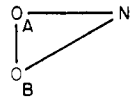


of antileukemic activity and critical distances between one nitrogen and two oxygen atoms such as in the general pattern **18** (or as applied to our general formulas **19** and **20**). This "triangulation" operation was performed on compounds **7a**, **7b**, **8**, and **15–17**. Calculation of the correlation coefficient (*r*)[12] showed significance at the 1–5% level which suggests a correlation. As was observed by Zee-Cheng and Cheng in the system examined we also did *not* find a correlation with activity and the O–N–O angle. A steric factor may be involved in which one methoxy function is forced from the plane of the arene ring causing unpredictable O–O bond lengths thereby creating errors in the calculated O–N–O angle. Additional effort is needed with many more examples to determine if such distances between heteroatoms and heteroatom angular relationships are of meaningful significance in predicting activity in a series.

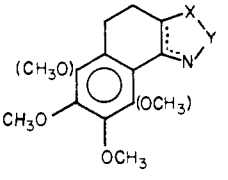
Table II. Percent Plating Efficiency of KB Cells vs. Concentration of Pyrazoles and Thiazole 17

Compd	Concn, μg/ml	% plating eff
7a	0-25	100
	50	91
	150-250	0
7b	0-12.5	100
	25	75
	50	14
	150	3
	250	0
15[a]	0-3	100
	12.5	81
	25	65
	50	31
	150-250	0
8	0-25	100
	50	70
	150	15
	250	0
16[a]	0-250	100
17[a]	50	56
	150	0

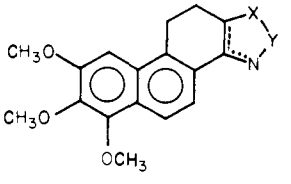
[a] See ref 9.



18



19



20

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-5A spectrophotometer as KBr pellets. NMR spectra were recorded in parts per million relative to standard Me_4Si on a Varian XL-100(15) high-resolution spectrometer in $DCCl_3$ unless otherwise indicated. Peak multiplicity is depicted as s for singlet, d for doublet, and t for triplet, p for pentet, and m for multiplet. Satisfactory ir and NMR spectra were obtained for all compounds reported. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical value. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Mass spectra were recorded on a CEC 21-110B double-focusing mass spectrometer (70 eV). Sodium methoxide was obtained from Research Organic/Inorganic Chemical Corp., Belleville, N.J., and 115% polyphosphoric acid (82.3% P_2O_5, guaranteed minimum) was obtained from FMC Corp. of New York, N.Y.

Microbial Screens. *B. subtilis* W23 and *P. fluorescens* were maintained on 0.5% glucose salts minimal medium. A weighed sample (~1 mg) of test compound was suspended in 0.5 ml of Me_2SO and diluted with H_2O (4.5 ml). Growth experiments were performed in tubes containing 5.0 ml of glucose–salt medium,[8] 0.5 ml of Me_2SO–test compound solution, and 0.2 ml of cell inoculum to give a final volume of 5.7 ml, which resulted in a final maximum concentration of 91 μg/ml for the test compound. The cultures were incubated for 12–14 hr at 37° with constant shaking and cell growth was measured by following the change in absorbance at 540 mm in a Coleman Junior II spectrophotometer (18-mm light path). Inhibition was shown by little or no change in optical density.

Tissue Culture Screens. Human tumor KB cells, originally obtained from Dr. Vernon Scott (University of Oklahoma Medical School), were grown at 37° using medium 199 supplemented with 10% calf serum.[8] A known weight of the test compound was dissolved in 0.05 ml of Me_2SO and 2.0 ml of H_2O added. An equal quantity of the Me_2SO–test compound solution and two times the medium containing the KB cells was incubated in a CO_2 gas-phase incubator (5% CO_2) at 37° for 7 days. After removal of the medium, the plates were washed with Hank's salt solution and the cells stained with 0.5% aqueous crystal violet. The colonies were counted microscopically and the relative plating efficiency was calculated using the control value of 100%.

3,4-Dihydro-6,7,8-trimethoxy-1(2*H*)-phenanthrone (2). Using a classical Reformatsky procedure, freshly distilled methyl 4-bromocrotonate (17.6 g, 0.98 mol) and 25.0 g (0.106 mol) of **1a** in 20 ml of anhydrous C_6H_6 and 50 ml of anhydrous ether were added to a mixture of 20 g (0.31 g-atom) of clean Zn (Fischer, sheets; cut 1 × 2 cm), 72 ml of anhydrous C_6H_6, and 1.3 g (0.0055 mol) of anhydrous $HgCl_2$. Upon heating, the mixture turned green and then red-orange in color. At 1.5-hr intervals, 10 g (0.15 g-atom) of clean Zn and 5.7 g (0.032 mol) of methyl 4-bromocrotonate were added until three additions were completed. Heating and stirring under N_2 were continued for 17 hr after the last addition. The mixture was then cooled, poured into ice–H_2O, neutralized (AcOH), and extracted (ether). Following evaporation of the solvents, the residual oil was distilled in vacuo. Crude methyl 4-(5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate (**3**) was collected (15.2 g) at 200–220° (0.5 mm). Crude **3** (9.88 g, 0.031 mol) was heated to 260° with 1.78 g of 10% Pd/C for 6 hr under a CO_2 atm. The mixture was cooled, diluted (50 ml of ether), filtered, and evaporated. After heating the residue at reflux for 12 hr with 3.8 g (0.082 mol) of KOH in 40 ml of 1:1 C_2H_5OH–H_2O, the hydrolyzate was diluted (H_2O), extracted (ether), and acidified (dilute HCl). The acidic solution was extracted (ether) and the ether was evaporated to yield crude **4**. Soxhlet extraction with hexanes yielded 7.65 g (81% from **3**) of **5** (mp 123–127°). A pure sample (mp 127–128°) of **4** crystallized from hexane. Compound **4** (5.8 g, 0.022 mol) was added to 30 g of 115% PPA (110°) and the mixture was stirred for 15 min. An additional 30 g of PPA was added and the mixture was reheated to 110°; it was then cooled with stirring to 60°. The resulting, dark-brown syrup was poured into 150 ml of 1:1 ice–H_2O, and the dark precipitate was dissolved in benzene. Purification through a column of alumina (Merck, neutral, C_6H_6) yielded 2.01 g (32.5% from **5**) of **2** as a light yellow solid (mp 135–137°). Sublimation gave a white, analytically pure sample of **2** (mp 137–139°): ir 5.98 (C=O), 9.06 μ (ArOCH$_3$); NMR δ 2.25 (p, 2 H, $CH_2CH_2CH_2$), 2.69 [t, 2 H, $CH_2CH_2CH_2C(O)$], 3.26 [t, 2 H, $CH_2CH_2CH_2C(O)$], 3.99 (s, 6 H, OCH_3), 4.01 (s, 3 H, OCH_3), 7.14 (s, 1 H, ArH), 7.98 (s, 2 H, ArH). Anal. ($C_{17}H_{18}O_4$) C, H.

3,4-Dihydro-2-(hydroxymethylene)-5,6,7-trimethoxy-1(2*H*)-naphthalenone (5a). Tetralone **1a**[5] (10.0 g, 0.0424 mol) was dissolved in 50 ml of anhydrous C_6H_6 and slowly added to a cooled (0–3°) mixture of $NaOCH_3$ (4.63 g, 0.085 mol) and 6.3 g (0.085 mol) of ethyl formate in 50 ml of anhydrous C_6H_6. After stirring (under N_2) at 0–3° for 1 hr, the mixture was stirred for 2 hr at room temperature. The resulting yellow gel was scooped into 200 ml of ice and stirred until the ice had dissolved. The organic layer was separated and washed (2 × 100 ml of H_2O, 1 × 75 ml of 5% NaOH). The aqueous washings were combined and washed (1 × 150 ml of C_6H_6; 1 × 150 ml of ether). Acidification (10% HCl) of the remaining aqueous layer and extraction with ether yielded an ethereal solution of crude **5a**. Evaporation of the ether and recrystallization (hexanes, bp 64–76°) of the residue gave pure **5a** (7.75 g, 69%): mp 74–76°; ir 2.75–3.10 (OH), 6.08 μ (C=O); NMR δ 2.32–3.54 (m, 4 H, CH_2CH_2), 3.85, 3.90, 3.95 (3 s, 9 H, OCH_3), 6.54 (s, 1 H, ArH), 8.10 (s, 1 H, C*H*OH), 14.4 (s, 1 H, CHO*H*); mass spectra (peak matching) *m/e* (rel intensity) 264.0998 [found 264.0989 (M^+, 100%)], 249.0762 [found 249.0762 ($M^+ - CH_3$, 20%)].

3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2*H*)-naphthalenone (5b). A solution of 2.5 g (0.0106 mol) of tetralone **1b**[6] in 40 ml of anhydrous C_6H_6 was added to a cooled (0–3°) mixture of $NaOCH_3$ (1.4 g, 0.0031 mol), ethyl formate (1.56 g, 0.0215 mol), and 10 ml of anhydrous C_6H_6. After stirring under N_2 at 0–3° for 1 hr and overnight at room temperature, the

reaction mixture was then worked up in identical fashion as for **5a**. Recrystallization (hexane), followed by sublimation [71° (0.02 mm)], yielded 1.12 g (38.5%) of pure **5b**: mp 69–71°; ir 2.90 (OH), 6.07 μ (C=O); NMR δ 2.33–2.90 (m, 4 H, CH_2CH_2), 3.87, 3.91, 3.96 (3 s, 9 H, OCH_3), 6.54 (s, 1 H, ArH), 8.10 (d, 1 H, CH), 14.3–14.7 (br s, 1 H, OH); mass spectra (peak matching) *m/e* (rel intensity) 264.0998 [found 264.0989 (M^+, 100%)], 235.1048 [found 236.1019 (M^+ – CO, 21%)].

3,4-Dihydro-2-(hydroxymethylene)-6,7,8-trimethoxy-1(2*H*)-phenanthrone (6). A solution of **2** (1.68 g, 0.0059 mol) in 15 ml of anhydrous C_6H_6 was slowly added to a cooled (0–3°) mixture of 10 ml of anhydrous C_6H_6, 1.0 g (0.023 mol) of $NaOCH_3$, and 1.37 g (0.018 mol) of ethyl formate. After stirring (under N_2) at 0–3° for 1 hr and then at room temperature for 3 hr, 60 ml of H_2O was added and the resulting two layers were separated. The organic layer was washed (H_2O) and the combined water layers were acidified (20% aqueous HCl). Cooling in an ice–H_2O bath caused precipitation of a yellow solid **6** (1.69 g, 91%) which was pure enough to use in subsequent reactions. Sublimation [140° (0.05 mm)] yielded pure **6**: mp 144.5–146.5°; ir 2.80–3.10 (OH), 6.10 μ (C=O); NMR δ 2.68 (t, J_{HH} = 8 Hz, 2 H, CH_2CH_2), 3.24 (t, J_{HH} = 8 Hz, 2 H, CH_2CH_2), 4.01, 4.04 (2 s, 9 H, OCH_3), 7.16 (s, 1 H, ArH), 7.88–8.01 (m, 2 H, ArH); mass spectra *m/e* (rel intensity) 314 (M^+, 100%).

4,5-Dihydro-6,7,8-trimethoxy-1*H*-benz[*g*]indazole (7a). The hydroxymethylene compound **5a** (5.1 g, 0.019 mol) was dissolved in 50 ml of anhydrous CH_3OH and 5.0 ml of anhydrous 97+% H_2NNH_2 was added. After stirring the exothermic reaction for 3.5 hr under N_2, 80 ml of H_2O was added, and the resulting solution was cooled overnight. Tan crystals formed and were isolated to give crude **7a** (3.4 g, 68%). Recrystallization (C_6H_6, hexane) gave pure **7a**: mp 94–95°; ir 3.25 (NH), 9.10 μ ($ArOCH_3$); NMR δ 2.60–3.02 (m, 4 H, CH_2CH_2), 3.74, 3.86, 3.88 (3 s, 9 H, OCH_3), 7.17 (s, 1, ArH), 7.33 (s, 1 H, CH), 7.40–7.76 (br s, 1 H, NH). Anal. ($C_{14}H_{16}N_2O_3$) N.

4,5-Dihydro-7,8,9-trimethoxy-1*H*-benz[*g*]indazole (7b). The hydroxymethylene compound **5b** (5.0 g, 0.019 mol) was dissolved in 20 ml of anhydrous CH_3OH; 6.8 g (0.21 mol) of anhydrous 95% H_2NNH_2 was added and the resulting solution was heated (50°) (2 hr). After returning to room temperature, the solution was stirred overnight. The resulting solution was poured into 40 ml of 1:1 ice–H_2O and stirred until a precipitate formed. Isolation of the tan solid by filtration, followed by sublimation [150° (0.2 mm)] and recrystallization (CH_3OH), gave 1.3 g (26%) of pure **7b**: mp 159–161°; ir 3.09 (NH), 9.18 μ ($ArOCH_3$); NMR δ 2.60–2.98 (m, 4 H, CH_2CH_2), 3.86, 4.01 (2 s, 9 H, OCH_3), 6.60 (s, 1 H, ArH), 7.41 (s, 1 H, CH), 8.78–9.02 (br s, 1 H, NH). Anal. ($C_{14}H_{16}N_2O_3$) N.

10,11-Dihydro-6,7,8-trimethoxy-3*H*-phenanthro[1,2-*c*]pyrazole (8). The hydroxymethylenephenanthrone **6** (1.55 g, 0.005 mol), 20 ml of anhydrous CH_3OH, and 1.5 ml (1.5 g, 0.48 mol) of 97+% H_2NNH_2 were stirred and boiled (under N_2) for 3.5 hr. After addition of 30 ml of H_2O, the mixture was heated for 20 min and then cooled in the refrigerator. The resulting precipitate was recrystallized from methanol and then sublimed [115° (0.05 mm)] to yield 1.1 g (72%) of pure **8**: mp 169–171°; ir 3.04 (NH), 8.99 μ ($ArOCH_3$); NMR δ 2.91 (t, J_{HH} = 7 Hz, 2 H, CH_2CH_2), 3.29 (t, J_{HH} = 7 Hz, 2 H, CH_2CH_2), 3.98, 4.00, 4.03 (3 s, 9 H, OCH_3), 7.16 (s, 1 H, ArH), 7.43 (s, 1 H, CH), 7.47 (s, 1 H, NH), 7.88 (d, J_{ortho} = 9 Hz, 1 H, ArH). Anal. ($C_{18}H_{18}N_2O_3$) N.

4,5-Dihydro-6,7,8-Trimethoxynaphth[1,2-*d*]isoxazole (9a). In a solution of 4.4 g (0.017 mol) of **5a** in 50 ml of glacial AcOH was added a solution of 1.16 g (0.017 mol) of $H_2NOH{\cdot}HCl$ and 1.37 g (0.017 mol) of NaOAc in 4 ml of H_2O. After heating to 100° with stirring under N_2 (1 hr), the mixture was cooled in an ice–H_2O bath and H_2O was added until precipitation was complete. The brown solid was filtered, washed (H_2O), and air-dried. Sublimation [95° (7.5×10^{-4} mm)] yielded 2.9 g (67%) of pure **9a**: mp 92–93°; ir 6.45 (C=N), 9.12 μ ($ArOCH_3$); NMR δ 2.58–3.10 (*m*, 4 H, CH_2CH_2), 3.86 (s, 3 H, OCH_3), 3.90 (s, 6 H, OCH_3), 7.05 (s, 1 H, ArH), 8.11 (s, 1 H, CH). Anal. ($C_{14}H_{15}NO_4$) C, H, N.

4,5-Dihydro-7,8,9-Trimethoxynaphth[1,2-*d*]isoxazole (9b). The hydroxymethylene compound **5b** (2.2 g, 0.0084 mol) was dissolved in 25 ml of glacial AcOH, and a solution of 0.69 g (0.0084 mol) of NaOAc and 0.58 g (0.0084 mol) of $H_2NOH{\cdot}HCl$ in 2 ml of H_2O was added. After heating (100°) under N_2 for 1 hr and cooling, the mixture was filtered to remove the solid that had formed in trace amount. Addition of water to the filtrate gave crude **9b** which was sublimed [100° (0.15 mm)] to give 1.2 g (55%) of pure **9b**: mp 128–130°; ir 6.30 (C=N), 9.20 μ ($ArOCH_3$); NMR δ 2.59–3.06 (m, 4 H, CH_2CH_2), 3.89, 4.00 (2 s, 9 H, OCH_3), 6.63 (s, 1 H, ArH), 8.11 (s, 1 H, CH). Anal. ($C_{14}H_{15}NO_4$) N.

10,11-Dihydro-7,8,9-trimethoxyphenanthro[1,2-*d*]isoxazole (10). To a mixture of **6** (1.03 g, 0.0033 mol) and 12.5 ml of glacial AcOH was added 0.24 g (0.0034 mol) of $H_2NOH{\cdot}HCl$ and 0.27 g (0.0034 mol) of NaOAc dissolved in 1 ml of H_2O. The resulting solution was heated to 100° for 1 hr and then allowed to cool to room temperature. Water was added with stirring, until precipitation ceased. The light tan solid was filtered out and washed (H_2O). Recrystallization from C_2H_5OH–acetone yielded 0.88 g (86%) of pure **10**: mp 142–143°; ir 6.25 (C=N), 8.96 μ ($ArOCH_3$); NMR δ 2.94 (t, J_{HH} = 8 Hz, 2 H, CH_2CH_2), 3.40 (t, J_{HH} = 8 Hz, 2 H, CH_2CH_2), 3.89, 4.00, 4.03 (3 s, 9 H, OCH_3), 7.11 (s, 1 H, ArH), 7.75 (d, J_{ortho} = 9 Hz, 1 H, ArH), 8.07 (d, J_{ortho} = 9 Hz, 1 H, ArH). Anal. ($C_{18}H_{17}NO_4$) N.

Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-oxo-2-naphthoate (11a). Tetralone **1a** (11.1 g, 0.47 mol) and 4.85 g (0.09 mol) of $NaOCH_3$ was dissolved in 50 ml of anhydrous dimethyl carbonate. After boiling for 3 hr, the solvent was evaported off and 50 ml of H_2O added to the residue. Following acidification (25% aqueous AcOH), extraction (2 × 30 ml, ether), and evaporation of the ether, the resulting oil was distilled in vacuo. Crude **11a**, suitable for use in subsequent reactions, was collected [10.2 g, 64%, bp 188–192° (0.4 mm)]. Crystallization from CH_3OH gave a pure sample of **11a**: mp 71–74°; ir 5.78 (ester C=O), 5.99 μ (keto C=O); NMR δ 2.14–3.08 (m, 4 H, CH_2CH_2), 3.47–3.67 (d of d, J_{HH} = 6, 9 Hz, 1 H, CH), 3.77 (s, 3 H, CO_2CH_3), 3.87, 3.89, 3.94 (3 s, 9, OCH_3), 7.38 (s, 1 H, ArH); mass spectra (peak matching) *m/e* (rel intensity) 294.1103 [found 294.1104 (M^+, 27%)], 236.1048 [found 236.1014 (M^+ – $C_2H_2O_2$, 100%)].

Methyl 1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methyl-1-oxo-2-naphthoate (11b). Tetralone **1a** (10.0 g, 0.058 mol), 4.0 g (0.089 mol) of $NaOCH_3$, and 100 ml (107 g, 1.2 mol) of anhydrous dimethyl carbonate were heated under N_2 (2 hr). A yellow suspension formed and was diluted with 200 ml of anhydrous CH_3OH. Iodomethane (10 ml, 22.7 g, 0.16 mol) was added and the mixture was boiled (1 hr). After coming to room temperature, the brown solution was acidified (2 *N* AcOH) and extracted (3 × 30 ml, ether). Evaporation of the ether and distillation yielded 13.35 g (71.5%) of slightly colored **11b**: bp 160–170° (0.3–0.5 mm); ir 5.79 (ester C=O), 5.96 μ (keto C=O); NMR δ 1.46 (s, 3 H, CH_3), 1.80–3.10 (m, 4 H, CH_2CH_2), 3.66 (s, 3 H, CO_2CH_3), 3.85, 3.89 (2 s, 9 H, OCH_3), 6.45 (s, 1 H, ArH); mass spectra (peak matching) *m/e* (rel intensity) 308.1260 [found 308.1258 (M^+, 30%)], 293.1025 [found 293.1034 (M^+ – CH_3, 100%)].

2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3*H*-benz[*g*]indazol-3-one (12a). The crude keto ester **11a** (3.75 g, 0.0127 mol) was dissolved in 5 ml of anhydrous CH_3OH; anhydrous 97+% H_2NNH_2 (4.1 ml, 4.1 g, 0.045 mol) was added, and the solution was boiled (1 hr). After cooling to room temperature, 30 ml of H_2O was added. Cooling produced a white precipitate. Filtration and sublimation [192° (0.003 mm)] of this solid gave 1.19 g (34%) of pure **12a**: mp 235–237°; ir 2.95–4.70 (OH, NH), 8.98 μ ($ArOCH_3$); NMR δ 2.38–2.90 (m, 4 H, CH_2CH_2), 3.75 (s, 6 H, OCH_3), 3.81 (s, 3 H, OCH_3), 7.10 (s, 1 H, ArH), 9.00–11.20 (br s, 1 H, NH, OH); mass spectra (peak matching) *m/e* (rel intensity) 276.1110 [found 276.1099 (M^+, 100%)], 261.0875 [found 261.0891 (M^+ – CH_3, 57%)].

2,3a,4,5-Tetrahydro-6,7,8-trimethoxy-3a-methyl-3*H*-benz[*g*]indazol-3-one (12b). To 13.35 g (0.046 mol) of **11b** was added 16.0 g (0.50 mol) of anhydrous 95% H_2NNH_2 and 10 ml of anhydrous CH_3OH. The mixture was heated to 50° for 1 hr and then stirred at room temperature for another 2 hr. The mixture was poured onto 50 ml of H_2O and a white precipitate formed immediately. After filtration, the crystals were triturated in ether, filtered out, and sublimed [172° (0.005 mm)] to yield 11.4 g (84.5%) of pure **12b**: mp 186–188°; ir 3.05–3.65 (OH, NH), 5.94 (C=O), 8.95 μ ($ArOCH_3$); NMR δ 1.34 (s, 3 H, CH_3), 1.58–2.34 (m, 2 H, CH_2CH_2), 2.80–3.04 (m, 2 H, CH_2CH_2), 3.90 (s, 9 H, OCH_3), 7.11 (s, 1 H, ArH), 9.26 (s, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_4$) N.

2,3a,4,5-Tetrahydro-7,8,9-trimethoxy-3a-methyl-3*H*-benz[*g*]indazol-3-one (12c). Tetralone **1b** (2.5 g, 0.011 mol) and 1.0 g (0.023 mol) of $NaOCH_3$ were dissolved in 25 ml (26.7 g, 0.296 mol) of anhydrous dimethyl carbonate. The mixture was boiled under N_2 (2 hr) and cooled before adding 25 ml of anhydrous CH_3OH and 1.5 ml (3.2 g, 0.022 mol) of CH_3I. After stirring 1 hr at 5°, the mixture was further stirred under N_2 overnight at room temperature. An additional 1.0 ml (2.1 g, 0.015 mol) of CH_3I was added, and the mixture was boiled (1 hr). After cooling, the mixture was acidified (25% aqueous AcOH); solvents were removed on a rotary evaporator. Water (25 ml) was added to the residue, and the solution was extracted with ether (3 × 30 ml). Evaporation of the ether left crude ester **11c**, a slightly colored oil, which crystallized upon standing. Recrystallization from C_2H_5OH–H_2O and sublimation [95° (2 mm)] gave pure methyl 1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-naphthoate (**11c**) (1.56 g, 48%): mp 82–84°; ir 5.79 (ester C=O), 5.98 μ (keto C=O); NMR δ 1.47 (s, 3 H, CH_3), 1.80–3.10 (m, 4 H, CH_2CH_2), 3.67 (s, 3 H, CO_2CH_3), 3.83, 3.88, 3.89 (3 s, 9 H, OCH_3), 6.45 (s, 1 H, ArH); mass spectra (peak matching) *m/e* (rel intensity) 308.1260 [found 308.1252 (M^+, 100%)], 293.1025 [found 293.1031 ($M^+ - CH_3$, 27%)].

The keto ester **11c** (1.35 g, 0.0044 mol) was dissolved in 2 ml of anhydrous CH_3OH and 1.4 g (0.044 mol) of anhydrous 97+% H_2NNH_2 was added. After heating (70°) the solution for 30 min under N_2, a solid formed. Water (7 ml) was added and the mixture was cooled (ice–H_2O bath). Isolation of the solid by filtration followed by sublimation [196° (0.003 mm)] gave 1.15 g (90% from **11c**) of pure **12c**: mp 224.5–225°; ir 2.80–3.70 (NH), 5.80 (C=O), 9.01 μ ($ArOCH_3$); NMR δ 1.31 (s, 3 H, CH_3), 1.62–3.22 (m, 4 H, CH_2CH_2), 3.88, 3.94 (2 s, 9 H, OCH_3), 6.52 (s, 1 H, ArH), 8.85 (s, 1 H, NH); mass spectra (peak matching) *m/e* (rel intensity) 290.1266 [found 290.1253 (M^+, 100%)], 275.1032 [found 275.1036 ($M^+ - CH_3$, 12%)].

2,10,11,11a-Tetrahydro-6,7,8-trimethoxy-11a-methyl-1*H*-phenanthro[1,2-*c*]pyrazol-1-one (14). A mixture of 1.46 g (0.0051 mol) of the phenanthrone **2**, 20 ml (21.3 g, 0.24 mol) of anhydrous dimethyl carbonate, and 1.0 g (0.023 mol) of $NaOCH_3$ was boiled (under N_2) for 15 min. The mixture solidified and could not be stirred. Anhydrous CH_3OH (30 ml) was added and the solid was broken up so stirring could be continued. Iodomethane (3 ml, 6.8 g, 0.048 mol) was added, and the mixture was boiled (1 hr). After cooling, the mixture was neutralized (AcOH), and most of the solvents were removed by evaporation. The residue was diluted (H_2O) and extracted (3 × 30 ml, ether). The combined ether extracts were dried ($MgSO_4$) and the ether was evaporated to yield 1.55 g (84.5%) of crude methyl 1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-oxo-2-phenanthrenecarboxylate (**13**). Sublimation [125° (0.05 mm)] gave pure **13**: mp 138–139°; ir 5.80 (ester C=O), 5.95 μ (keto C=O); NMR δ 1.55 (s, 3 H, CH_3), 1.98–3.40 (m, 4 H, CH_2CH_2), 3.63 (s, 3 H, CO_2CH_3), 4.00, 4.03 (2 s, 9 H, OCH_3), 7.11 (s, 1 H, ArH), 8.00 (s, 2 H, ArH); mass spectra *m/e* (rel intensity) 358 (M^+, 100%).

The crude ester **13** (1.03 g, 0.0029 mol), 0.9 ml (0.9 g, 0.03 mol) of anhydrous 97+% H_2NNH_2, and 5 ml of anhydrous CH_3OH were combined and heated to 60° under N_2 for 1 hr. This solution was poured over 1:1 ice–H_2O and extracted (50 ml of ether). Sublimation [165° (0.05 mm)] of the residue, after evaporation of the ether, gave 56 mg (32.2% from **2**) of pure **14**: mp 205–206°; ir 3.18 (NH), 5.90 (C=O), 8.94 μ ($ArOCH_3$); NMR δ 1.38 (s, 3 H, CH_3), 1.66–3.42 (m, 4 H, CH_2CH_2), 4.01 (s, 6 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.06 (s, 1 H, ArH), 7.76 (d, J_{ortho} = 9 Hz, 1 H, ArH), 8.05 (d, J_{ortho} = 9 Hz, 1 H, ArH), 8.84–8.99 (br s, 1 H, NH). Anal. ($C_{19}H_{21}N_2O_4$) N.

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