1,4-Dimethylpyrano[2,3-*c*]pyrazole-3-acetic Acid (14b). Compound **13b** (2.5 g, 0.01 mol) was treated as in the preparation of **14a**, to afford **14b**: yield 1.7 g (80%); mp 213–214 °C dec. Anal. ($C_{10}H_{10}N_2O_4$) C, H, N.

Analgesic Assay.[3,4] Phenylquinone writhing was induced by phenylquinone (0.03% in 5% ethanol aqueous solution), 10 mL/kg, ip, in female mice (18–22 g) of ddN strain. The number of writhes was counted for 15 min, beginning 5 min after phenylquinone injection. Each compound was administered orally 30 min before phenylquinone. Five to ten mice were used for each dose.

Antiinflammatory Activity.[5] Hind-paw edema was induced by a subcutaneous injection of 0.1 mL of a 1% carrageenin solution into the hind foot pad of male rats (90–120 g) of Wistar strain. Each compound was administered orally 1 h before carrageenin injection. Five to ten rats were used for each dose.

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Registry No. **1**, 5203-98-5; **2** (R = CH_3), 60-34-4; **2** (R = C_2H_5), 624-80-6; **2** (R = C_3H_7), 5039-61-2; **2** [R = $(CH(CH_3)_2]$, 2257-52-5; **2** [R = $(CH_2)_3CH_3]$, 3530-11-8; **2** [R = $CH_2CH(CH_3)_2]$, 42504-87-0; **2** [R = $(CH_2)_4CH_3]$, 2656-71-5; **3a**, 5775-94-0; **3b**, 88549-98-8; **3c**, 88549-99-9; **3d**, 88550-00-9; **3e**, 88550-01-0; **3f**, 88550-02-1; **4a**, 87343-65-5; **4b**, 88563-11-5; **4c**, 88550-03-2; **4d**, 88550-04-3; **4e**, 88550-05-4; **4f**, 88550-06-5; **5**, 88550-07-6; **6**, 67056-25-1; **7**, 88550-08-7; **8**, 88550-09-8; **9a**, 88550-10-1; **9c**, 88550-11-2; **11a**, 88550-12-3; **11b**, 88550-13-4; **11c**, 88550-14-5; **11d**, 88550-15-6; **12a**, 88550-16-7; **12b**, 88563-12-6; **13a**, 64518-00-9; **13b**, 64518-02-1; **14a**, 88550-17-8; **14b**, 88550-18-9; 2-furoyl chloride, 527-69-5; 2-chloroethanol, 107-07-3; (2-hydroxyethyl)hydrazine, 109-84-2; chloroacetyl chloride, 79-04-9; benzoyl chloride, 98-88-4; $EtOCOCH_2COCH_2COOEt$, 105-50-0; CH_3COCH_2COOEt, 141-97-9.

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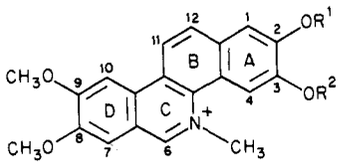
Synthesis and Biological Activity of Structural Analogues of the Anticancer Benzophenanthridine Alkaloid Nitidine Chloride

Mark Cushman,* Prem Mohan, and Edward C. R. Smith

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907. *Received June 24, 1983*

The indenoisoquinoline analogue **9** of nitidine (**1**) has been prepared and found to possess significant anticancer activity against L1210 lymphoid leukemia, P388 lymphocytic leukemia, and B16 melanocarcinoma. Analogue **14**, which lacks the B ring of nitidine (**1**), has also been synthesized. Compound **14** retains the in vitro toxicity associated with nitidine (**1**) but is devoid of antileukemic activity. The structural factors that may contribute to the difference in biological activity between the two closely related analogues **9** and **14** are discussed.

Nitidine (**1**) and fagaronine (**2**) are benzophenanthridine



1, $R^1 + R^2 = CH_2$
2, $R^1 = H$, $R^2 = CH_3$

alkaloids that have been isolated from *Zanthoxylum nitidum*[1,2] and *Fagara zanthoxyloides*,[3] respectively. The structure of nitidine (**1**) was established by its conversion to known compounds[2] and by the synthesis of dihydronitidine,[4,5] while the structure of fagaronine (**2**) was originally proposed on the basis of spectral evidence[3,6] and was later confirmed by total sythesis.[7] Several nitidine (**1**) syntheses have also been performed.[4,5,8]

Both nitidine (**1**) and fagaronine (**2**) have displayed activity against the mouse leukemia L1210 and P388 systems.[3,9,10] Nitidine (**1**) has also shown curative activity against Lewis lung carcinoma.[9b] The anticancer activity of these compounds and related benzophenanthridine alkaloids has been correlated with inhibition of reverse transcriptase activity of RNA tumor viruses by binding to the A-T base pairs of the template primers,[11] inhibition of transfer RNA methyltransferase,[12] and the iminium ion

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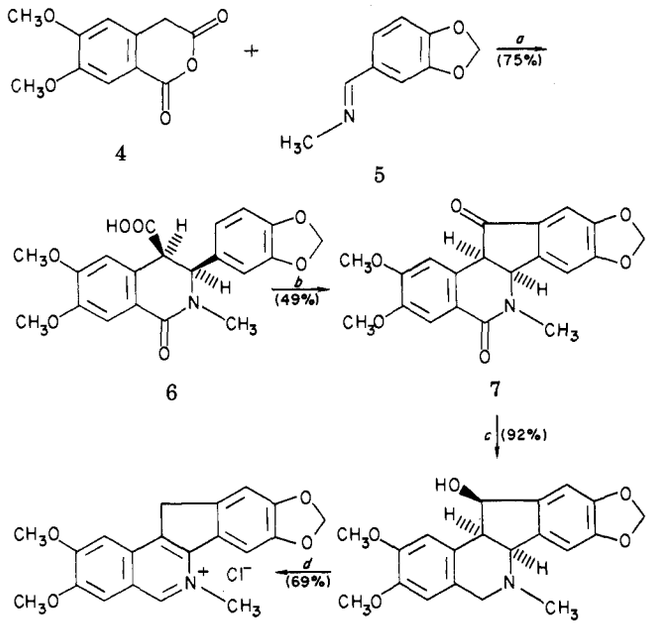
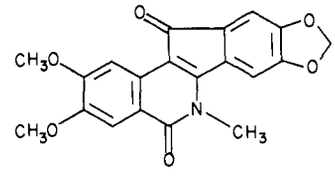
Scheme I



[a] $CHCl_3$, room temperature (0.5 h). [b] PPA, 70–80 °C (1 h). [c] $LiAlH_4$, THF, reflux (20 h). [d] (1) 5% Pd/C, AcOH, reflux (20 h); (2) aqueous NaCl.

⇄ alkanolamine equilibrium position.[13] Nitidine (1) is inactive against a strain of P388 leukemia that was developed to be resistant to adriamycin.[14] Since the potential clinical usefulness of the known antitumor benzophenanthridine alkaloids is hampered by their acute toxicity, there is interest in the synthesis of structurally related compounds that might have a more favorable therapeutic index.[9b,10,15]

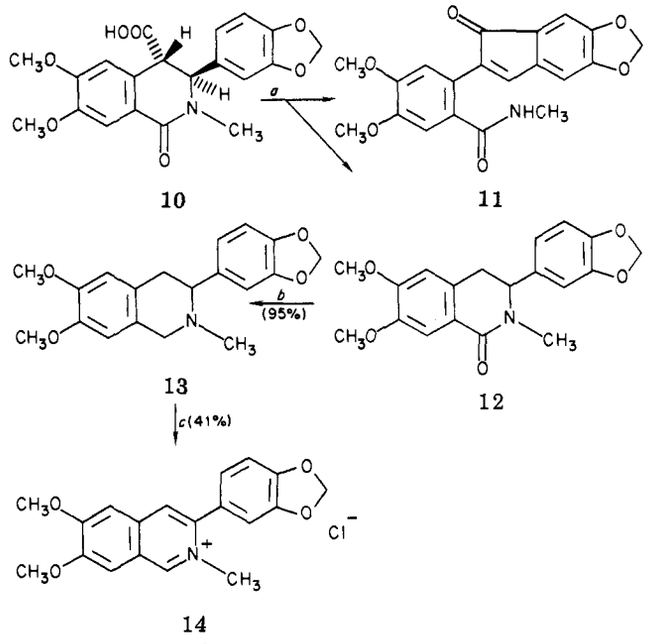
During our work on the development of a total synthesis of nitidine chloride,[8e] the unusual oxidative conversion of the cis acid 6 (Scheme I) to the indenoisoquinoline 3 by



thionyl chloride was discovered.[16] This accidental observation suggested the possibility of preparing indenoisoquinoline analogues of the anticancer benzophenanthridine alkaloids. We now report the synthesis of the active indenoisoquinoline analogue 9 of nitidine (1), as well as analogue 14, which retains in vitro cytotoxicity but is devoid of anticancer activity.

Chemistry. The synthesis of compound 9 is outlined in Scheme I. The previously reported condensation of 4,5-dimethoxyhomophthalic anhydride (4) with piperonylidenemethylamine (5) yielded intermediate 6, as well as the corresponding trans diastereomer 10 (Scheme II), which was obtained in this instance in 25% yield.[8e] The intramolecular Friedel–Crafts cyclization of 6 using polyphosphoric acid afforded the desired product 7. Treatment of compound 7 with lithium aluminum hydride reduced both the ketone and lactam functionalities to give the amino alcohol 8. Dehydration, as well as dehydrogenation, of intermediate 8 occurred upon subjection to palladium on charcoal in refluxing acetic acid. The attractive features of this route are that it proceeds from readily available starting materials in only four steps and provides the desired product in 23% overall yield. Modification of this synthesis might therefore be expected to provide other related indenoisoquinolines for biological evaluation.

Scheme II



[a] 220 °C (4 h). [b] $LiAlH_4$, THF, reflux (24 h). [c] (1) 5% Pd/C, AcOH, reflux (40 h); (2) aqueous NaCl.

During the synthesis of compound 9, an unusual dehydrogenation reaction of intermediate 7 to yield 3 was observed under basic conditions. This transformation was found to occur when 7 was simply heated with potassium ethoxide in refluxing ethanol. It is unlikely that molecular oxygen is involved in this conversion, since the reaction was observed to proceed even after the solution was purged overnight with nitrogen. The conjugation of the stable tetrasubstituted double bond of 3 with both aromatic rings, as well as the carbonyl group, undoubtedly stabilizes the transition state leading to this product.

In order to delineate further the structural parameters associated with the cytotoxicity and anticancer activity of nitidine (1) and related alkaloids, we prepared analogue 14 (Scheme II), which lacks the B ring. The trans diastereomer 10, which proved to be useless in the synthesis of the indenoisoquinoline 9, was utilized as the starting material. The thermolysis of 10 at 220 °C for 4 h yielded a mixture of products from which compounds 11 and 12 could be isolated in 10 and 30% yields, respectively. Lithium aluminum hydride reduction of the lactam functionality of 12 afforded the amine 13, which then yielded 14 after dehydrogenation with palladium on charcoal in refluxing acetic acid.

Biological Results and Discussion

Both compounds 9 and 14 displayed significant cytotoxicities in the in vitro KB cell culture system (ED_{50} =

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Table I. Evaluation of Compounds 9 and 14 for Anticancer Activity in Survival Tumor Systems[a,f]

tumor	compd	dose, mg/kg	survival	wt diff	% T/C
L1210[b]	9	100	6/6	-5.8	95
		50	6/6	-5.8	198
		25	6/6	-5.4	165
		12.5	6/6	-2.6	156
		6.25	6/6	-3.2	154
		3.12	6/6	-1.9	129
P388[c]	9	200	0/6		
		100	5/5	-5.8	168
		50	5/5	-5.0	149
		25	5/5	-3.6	151
		12.5	5/5	-1.4	134
B16[d]	9	200	4/10	-4.2	
		100	7/10	-4.6	120
		50	10/10	-4.9	147
		25	10/10	-2.5	139
		12.5	9/10	-1.0	131
		6.25	10/10	-0.5	148
LL[e]	9	200	2/10	-4.9	
		100	10/10	-3.8	51
		50	10/10	-2.6	119
		25	10/10	-2.4	114
		12.5	10/10	-0.9	97

[a] For the general screening procedure and data interpretation, see R. I. Geran et al.[19] and Instruction Booklet 14, "Screening Data Summary Interpretation and Outline of Current Screen"; Drug Evaluation Branch, Division of Cancer Treatment, National Cancer Institute; Bethesda, MD, revised June 1980. [b] L1210 lymphoid leukemia. [c] P388 lymphocytic leukemia. [d] B16 melanocarcinoma. [e] Lewis lung carcinoma. [f] Compound 14 was inactive in the P388 lymphocytic leukemia system at a dose of 200 mg/kg.

0.038 and 0.005 μg/mL, respectively).

Examination of the data presented in Table I reveals that the indenoisoquinoline analogue 9 of nitidine possesses promising activity against L1210 lymphoid leukemia, P388 lymphocytic leukemia, and B16 melanocarcinoma. The optimal T/C value of 198 for the analogue in the L1210 system compares favorably with the corresponding value of 136 for nitidine chloride itself.[9b] However, in the P388 system the relative activities are reversed, with nitidine chloride (optimal T/C = 209) being more active than the analogue 9 (optimal T/C = 168). The inactivity of compound 9 against Lewis lung carcinoma (optimal T/C 119 at 50 mg/kg) also contrasts with the reported curative activity of nitidine chloride.[9b] The activity of analogue 9 against B16 melanocarcinoma is comparable to that of nitidine chloride (optimal T/C = 141 at 20 mg/kg).[17] These results show that the biological activity profile is affected by the small structural change in going from nitidine (1) to the analogue 9, with the analogue being more active against some tumors and less active against others. The analogue 9 also appears to be less active than fagaronine (optimal T/C = 265[3]) against P388 lymphocytic leukemia. In contrast, compound 14 shows no antileukemic activity in the P388 lymphocytic leukemia test system.

Compound 9 was also tested for anticancer activity in several tumor inhibition systems (Table II). It possesses no activity in the colon 38 and $CD8F_1$ mammary tumor systems and only marginal activity against the MX-1 breast xenograph.

Whereas compound 9 retains the planarity of nitidine (1) and should therefore be capable of DNA intercalation, the plane of the methylenedioxyphenyl substituent of 14

(17) NCI screening data summaries for NSC 146397.

Table II. Evaluation of Analogue 9 for Anticancer Activity in Tumor Inhibition Systems[a]

tumor	compd	dose, mg/kg	survival	wt diff	% T/C
MX-1[b]	9	600	0/6		
		300	1/6		
		150	5/6	-6.0	35
		75	4/6	-4.5	102
C8[c]	9	800	0/10		
		400	10/10	-6.2	85
		200	10/10	-4.3	97
		100	10/10	-1.9	107
		50	10/10	-0.8	94
$CD8F_1$[d]	9	500	0/10		
		250	2/10		
		125	10/10	-3.2	105
		62	10/10	-1.0	92

[a] In general, a minimal reproducible tumor inhibition of test over control animals resulting in a T/C ≤ 42% is necessary for further experimental testing. [b] MX-1 breast xenograph. [c] Colon 38. [d] $CD8F_1$ mammary tumor.

is without doubt primarily not coplanar with the isoquinoline ring due to a nonbonded interaction between the *N*-methyl group and the ortho hydrogens of the methylenedioxyphenyl ring. This effect is well-known in twisted biphenyls and is supported in the present instance by NMR data. The *N*-methyl group of 9 is deshielded by the adjacent coplanar methylenedioxyphenyl ring, causing the corresponding NMR signal to appear at δ 4.66, while that of 14 occurs upfield at δ 4.14. This lack of coplanarity may prevent the intercalation of 14 with DNA,[18] although the electrophilic iminium functionality of 14 should still be capable of being attacked by biological nucleophiles.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 80-MHz spectrometer in $CDCl_3$, except where noted. High-resolution 470-MHz NMR spectra were obtained by using a Nicolet NTC-470 spectrometer, and the data were accumulated by using 32K free induction decays. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Analytical thin-layer chromatography (TLC) was performed on Baker-flex silica gel 1B2-F sheets. Microanalyses were obtained from the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnegan 4000 spectrometer using an ionization potential of 70 eV. The chemical ionization mass spectra (CIMS) were obtained by using isobutane as the reagent gas. Organic extracts were dried by using Na_2SO_4, except where noted.

***cis*-2,3-Dimethoxy-5,6,12,13-tetrahydro-5,11-dioxo-6-methyl-8,9-(methylenedioxy)-11*H*-indeno[1,2-*c*]isoquinoline (7).** The cis acid 6[8e] (2.10 g, 5.45 mmol) was mechanically stirred with polyphosphoric acid (21.0 g) at 70–80 °C for 1 h. After the mixture was cooled, water (200 mL) was added, and the mixture was stirred for 10 min. The mixture was extracted with chloroform (2 × 100 mL). The combined chloroform layers were washed with 5% sodium bicarbonate (2 × 100 mL) and water (2 × 200 mL), dried, and filtered, and the filtrate was evaporated to give a pinkish-red solid (0.98 g, 49%): mp 270–275 °C. An analytical sample was prepared by recrystallization from chloroform–methanol (1:1) to yield white prisms: mp 276–278 °C (lit.[16] mp 270–272 °C); IR (KBr) 1700, 1650, 1600, 1475, 1265, 1030 cm^{-1}; NMR δ 7.59 (s, 1 H), 7.18 (s, 1 H), 7.08 (s, 1 H), 7.05 (s, 1 H), 6.07

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(m, 2 H), 5.13 (d, 1 H, J = 7.2 Hz), 4.22 (d, 1 H, J = 8.0 Hz), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.50 (s, 3 H).

Conversion of Intermediate 7 to 2,3-Dimethoxy-5,6-dihydro-5,11-dioxo-6-methyl-8,9-(methylenedioxy)-11*H*-indeno[1,2-*c*]isoquinoline (3). A mixture containing the keto amide 7 (50 mg, 0.14 mmol), potassium ethoxide (25 mg, 0.30 mmol), and absolute ethanol (5 mL) was purged with nitrogen overnight and then heated at reflux for 3 h. After the mixture was cooled, water (10 mL) was added, and the suspension was extracted with chloroform (3 × 20 mL). The chloroform layers were washed with 5% acetic acid (3 × 30 mL) and water (30 mL) and then dried and filtered, and the filtrate was evaporated to dryness to yield a reddish-brown residue (49 mg, 96%). Recrystallization, by dissolving in chloroform and slowly adding methanol, afforded red prisms: mp 296–298 °C dec (lit.[16] mp 295–299 °C dec); IR (KBr) 1680, 1640, 1470, 1275, 1240, 1010 cm^{-1}; NMR δ 7.95 (s, 1 H), 7.62 (s, 1 H), 7.09 (s, 1 H), 7.03 (s, 1 H), 6.07 (s, 2 H), 4.03 (s, 3 H), 3.97 (s, 3 H), 3.95 (s, 3 H).

2,3-Dimethoxy-5,6,12α,13α-tetrahydro-11β-hydroxy-6-methyl-8,9-(methylenedioxy)-11*H*-indeno[1,2-*c*]isoquinoline (8). The keto amide 7 (1.35 g, 3.67 mmol) was heated at reflux with lithium aluminum hydride (295 mg, 7.77 mmol) in freshly dried and distilled THF (115 mL) for 20 h. After cooling in ice, the reaction mixture was quenched by successively adding water (1 mL), 15% sodium hydroxide (1 mL), and water (3 mL). Chloroform (75 mL) was added, and the mixture was stirred for 10 min and filtered. The precipitate was washed with chloroform (2 × 25 mL), the combined filtrates were dried and filtered, and the filtrate was evaporated to leave a pink residue (1.20 g, 92%). Recrystallization from benzene gave a pink powder. A second crop yielded additional product: yield 0.80 g (61%); mp 197–199 °C; IR (KBr) 3340, 2920, 1600, 1500, 1460, 1345, 1320, 1280, 1120, 1010 cm^{-1}; NMR (470 MHz) δ 7.00 (s, 1 H), 6.86 (s, 1 H), 6.79 (s, 1 H), 6.60 (s, 1 H), 5.97 (d, 1 H, J = 1.2 Hz), 5.96 (d, 1 H, J = 1.2 Hz), 4.86 (d, 1 H, J = 5.2 Hz), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.81 (d, 1 H, J = 15.0 Hz), 3.48 (d, 1 H, J = 14.6 Hz), 3.39 (s, 1 H), 3.38 (d, 1 H, J = 5.2 Hz), 2.36 (s, 3 H); CIMS, m/e (relative intensity) 356 (M^+ + 1, 100), 338 (60), 324 (5). Anal. ($C_{20}H_{21}NO_5$) C, H, N.

2,3-Dimethoxy-6-methyl-8,9-(methylenedioxy)-11*H*-indeno[1,2-*c*]isoquinolinium Chloride (9). The cis amino alcohol 8 (0.75 g, 2.11 mmol) was heated at reflux with 5% palladium on charcoal (265 mg) in glacial acetic acid (150 mL) for 20 h. After cooling, the mixture was filtered through Celite, and the solvent was evaporated to give a green-yellow solid. The residue was dissolved in water (60 mL) and ethanol (12 mL) to give a green solution, to which was added 15% aqueous sodium chloride (10 mL). A yellow product precipitated immediately and was filtered, washed with water (25 mL), and dried over phosphorus pentoxide under vacuum overnight to yield a yellow powder (0.57 g, 69%). An analytical sample was recrystallized from aqueous MeOH: mp 300–302 °C dec; IR (KBr) 3380, 1480, 1305, 1210, 1000 cm^{-1}; NMR (Me_2SO-d_6) δ 9.45 (s, 1 H), 7.83 (s, 1 H), 7.66 (s, 1 H), 7.65 (s, 1 H), 7.54 (s, 1 H), 6.21 (s, 2 H), 4.66 (s, 3 H), 4.33 (s, 2 H), 4.10 (s, 3 H), 3.99 (s, 3 H); EIMS, m/e (relative intensity) 335 (73), 321 ($M^+ - CH_3Cl$, 100), 306 (9), 190 (6), 177 (6), 161 (14), 75 (16). Anal. ($C_{20}H_{18}NO_4Cl\cdot H_2O$) C, H, N, Cl.

***N*-Methyl-3-[3,4-(methylenedioxy)phenyl]-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolinone (12).** The trans acid 10[8e] (2 g, 5.19 mmol) was heated at 220 °C for 4 h. The residue was dissolved in a minimum amount of chloroform and subjected to column chromatography on silica gel (150 g, ethyl acetate as eluent). The second group of fractions (R_f 0.50, silica gel TLC, ethyl acetate) gave a pale yellow residue (0.53 g, 30%), which was recrystallized from benzene–hexane to give yellow crystals: mp 206–207 °C; IR (KBr) 2930, 1625, 1595, 1500, 1475, 1430, 1360, 1230, 1015 cm^{-1}; NMR (470 MHz) δ 7.62 (s, 1 H), 6.67 (d, 1 H, J = 8.6 Hz), 6.54 (d, 1 H, J = 7.2 Hz), 6.53 (s, 1 H), 6.46 (s, 1 H), 5.90 (d, 1 H, J = 1.3 Hz), 5.89 (d, 1 H, J = 1.4 Hz), 4.62 (d of d, 1 H, J = 7.1 and 2.9 Hz), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.57 (d of d, 1 H, J = 15.8 and 6.9 Hz), 3.05 (s, 3 H), 2.87 (d of d, 1 H, J = 15.7 and 2.7 Hz); CIMS, m/e (relative intensity) 343 (5), 342 (M^+ + 1, 23), 58 (100). Anal. ($C_{19}H_{19}NO_5$) C, H, N.

5,6-(Methylenedioxy)-2-[2-(methylcarbamoyl)-4,5-dimethoxyphenyl]-1*H*-inden-1-one (11). The column above also gave a first group of fractions (R_f 0.83, silica gel TLC, ethyl acetate) from which solid began to crystallize out of ethyl acetate on standing. Evaporation of the solvent gave an orange residue (0.19 g, 10%), which on recrystallization from benzene–hexane gave orange-yellow crystals: mp 225–226 °C; IR (KBr) 3400, 1675, 1640, 1585, 1200, 1005 cm^{-1}; NMR δ 8.05 (s, 1 H), 7.62 (s, 1 H), 7.13 (s, 1 H), 6.94 (s, 1 H), 6.86 (s, 1 H), 5.99 (s, 2 H), 3.95 (s, 3 H), 3.53 (s, 3 H), 3.42 (s, 3 H); CIMS, m/e (relative intensity) 370 (6), 369 (12), 368 (M^+ + 1, 52), 58 (100). Anal. ($C_{20}H_{17}NO_6$) C, H, N.

***N*-Methyl-3-[3,4-(methylenedioxy)phenyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13).** The amide 12 (50 mg, 0.15 mmol) was heated at reflux with lithium aluminum hydride (56 mg, 1.48 mmol) in freshly dried and distilled THF (12 mL) for 24 h. The reaction mixture was quenched by cooling in ice and successively adding water (60 μL), 15% sodium hydroxide (60 μL), and water (180 μL). After the mixture was stirred for 15 min, chloroform (20 mL) was added; the mixture was stirred for 45 min and filtered, and the filtrate was dried and evaporated to dryness to yield an orange-brown solid (46.9 mg, 95%), mp 54–58 °C, which without further purification was carried on to the next step.

***N*-Methyl-3-[3,4-(methylenedioxy)phenyl]-6,7-dimethoxyisoquinolinium Chloride (14).** The tertiary amine 13 (0.75 g, 2.29 mmol) was heated at reflux with 5% palladium on charcoal (550 mg) and glacial acetic acid (135 mL) for 40 h. After cooling, the reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. The residue was dissolved in water (1.5 mL), and to the solution was added 15% aqueous sodium chloride (3 mL). The solution was refrigerated for 1 h, during which time crystallization occured. The product was filtered to obtain a greenish-white powder (382 mg, 41%), mp 189–191 °C. An analytical sample was prepared by dissolving in chloroform and slowly adding ether: mp 191–193 °C; IR (KBr) 3400, 1600, 1490, 1270, 1240, 1220 cm^{-1}; NMR (Me_2SO-d_6) δ 9.73 (s, 1 H), 8.19 (s, 1 H), 7.99 (s, 1 H), 7.73 (s, 1 H), 7.29 (s, 1 H), 7.19 (s, 2 H), 6.18 (s, 2 H), 4.14 (s, 3 H), 4.05 (s, 3 H), 4.02 (s, 3 H); CIMS, m/e (relative intensity) 312 (6), 311 (20), 310 (M^+ + 1 − CH_3Cl, 100), 296 (18). Anal. ($C_{19}H_{18}NO_4Cl\cdot 2.5H_2O$) C, H, N, Cl.

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