9 H, α-H, aromatic H, tropolone H, NH), 9.2 (br s, 1 H, OH). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

Compounds **31** and **32** were prepared in the same manner.

3-[α-(Benzoylamino)-4-methoxybenzyl]-6-isopropyltropolone (31): mp 172–173 °C (from CH_2Cl_2–MeOH); yield 53%; NMR ($CDCl_3$) δ 1.31 (d, 6 H, CHMe_2, J = 7 Hz), 2.5–3.3 (m, 1 H, CHMe$_2$), 3.79 (s, 3 H, OMe), 6.4–8.2 (m, 12 H, α-H, aromatic H, tropolone H, NH), 8.60 (d, 2 H, aromatic H, J = 9 Hz), 8.2–8.8 (br s, 1 H, OH). Anal. ($C_{25}H_{25}NO_4$) C, H, N.

3-[α-(2-Hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]benzoxazoline-2-thione (32): mp 163–166 °C (from CH_2Cl_2–MeOH); yield 41%; IR (Nujol) 3150; NMR ($CDCl_3$) δ 1.30 (d, 6 H, CHMe_2, J = 7 Hz), 2.5–3.2 (m, 1 H, CHMe$_2$), 3.81 (s, 3 H, OMe), 6.7–8.0 (m, 1 H, aromatic H), 8.3–9.3 (br, 1 H, OH); MS, m/z 433 (M^+). Anal. ($C_{25}H_{23}NO_4S$) C, H, N.

3-[α-(Phenylthio)benzyl]-6-isopropyltropolone (33). A mixture of hinokitiol (**1**; 2 g, 12.2 mmol) and benzaldehyde diphenyl thioacetal (6.0 g, 19.5 mmol) was heated at 160 °C for 7 h under an argon atmosphere. The reaction mixture was chromatographed on silica gel with petroleum ether–AcOEt (25:1) to give **33** (1.5 g, 34%): mp 105–106 °C (from MeOH); IR (Nujol) 3200 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (d, 6 H, CHMe_2, J = 7 Hz), 2.6–3.2 (m, 1 H, CHMe$_2$), 6.58 (s, 1 H, α-H), 6.8–8.2 (m, 13 H, aromatic H, tropolone H), 8.5–9.5 (br, 1 H, OH); MS, m/z 362 (M^+). Anal. ($C_{23}H_{22}O_2S$) C, H.

Biological Assays. Assays of antitumor activity were carried out as described previously.[1]

Registry No. **1**, 499-44-5; **3b**, 96292-82-9; **5**, 75802-22-1; **6**, 77317-00-1; **7**, 77316-99-5; **8**, 96292-83-0; **9**, 96292-84-1; **10**, 96292-85-2; **11**, 82584-05-2; **12**, 96292-86-3; **13**, 96292-87-4; **14**, 96292-88-5; **15**, 96292-89-6; **16**, 96292-90-9; **17**, 96292-91-0; **18**, 96292-92-1; **19**, 22876-19-3; **20**, 96292-93-2; **21**, 95-25-0; **22**, 96292-94-3; **23**, 96292-95-4; **24a**, 774-48-1; **24b**, 2403-58-9; **25**, 96292-96-5; **26**, 96292-97-6; **27**, 96292-98-7; **28**, 96306-50-2; **29**, 96306-51-3; **30**, 96292-99-8; **31**, 96293-00-4; **32**, 96293-01-5; **33**, 96293-02-6; B_3NH_2, 55-21-0; Boz-H, 2382-96-9; 1,2-dihydroinden-1-one, 480-90-0; 1-isochromancarboxylic acid, 13328-85-3; thymol, 89-83-8; kojic acid, 501-30-4; 2-methoxy-4-allylphenol, 97-53-0; 2-hydroxy-1,4-naphthalenedione, 83-72-7; acetamide, 60-35-5; benzaldehyde diphenyl dithioacetal, 7695-69-4; 5-methyl-2-isopropylphenol, 89-83-8; benzylcarbonylbenzene, 451-40-1; 4-hydroxy-1-benzopyran-2-one, 1076-38-6; 3-acetyl-4-hydroxy-3-pyrrolin-2-one, 2113-93-1.

Synthesis and Antitumor Activity of Structural Analogues of the Anticancer Benzophenanthridine Alkaloid Fagaronine Chloride

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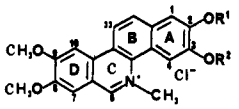
The indenoisoquinoline analogue **4** of fagaronine chloride (**2**) has been prepared, as well as its positional isomer **20** and the corresponding mesylated derivatives **16** and **19**. Compounds **4**, **16**, and **20** were tested against P388 lymphocytic leukemia and found to possess significant activity. A tricyclic analogue **24** was also synthesized and was devoid of cytotoxicity in the KB cancer cell culture system. The change in the substitution pattern of the A-ring on going from **4** to **20** was tolerated without producing a significant decrease in antitumor activity.

The benzo[*c*]phenanthridine alkaloids nitidine (**1**) and fagaronine (**2**) have been isolated from *Zanthoxylum nitidum*[1,2] and *Fagara zanthoxyloides*,[3] respectively. The structure elucidation of nitidine (**1**) involved its chemical conversion to known compounds[2] as well as the synthesis of dihydronitidine,[4] while that of fagaronine (**2**) was proposed after NMR analysis of its *N*-demethyl derivative[5] and confirmed by total synthesis.[6] Nitidine (**1**) has also been synthesized by several methods.[4,7]



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

Recent interest in nitidine (**1**) and fagaronine (**2**) has been stimulated by their activity against the mouse Leu-

Table I. Evaluation of the Indenoisoquinoline Analogue **3** of Nitidine (**1**) for Anticancer Activity in the M5076 Sarcoma System[a]

compd	dose, mg/kg	survival	wt diff	% T/C
3	400	0/10		
	200	6/10	−7.2	
	100	9/9	−4.4	137
	50	9/9	−2.0	107
	25	10/10	−0.3	113
	12.5	10/10	−0.2	109
	6.25	10/10	−0.8	115

[a] For the general screening procedure and data interpretation, see ref 19.

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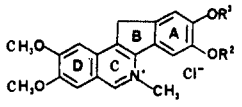
kemia L1210 and P388 systems.[3,8,9] Both compounds, as well as several structurally related substances, inhibit reverse transcriptase activity of RNA tumor viruses, and the fact that this effect is observed selectively with A:T and not with G:C template primers has been interpreted to indicate a stronger binding to the A:T base pairs.[10] However, more recent work has demonstrated significant binding of fagaronine (2) to a synthetic poly(dG) poly(dC) ribonucleotide.[11] Nitidine (1) has displayed inhibitory activity against both catechol *O*-methyltransferase and transfer RNA methyltransferases.[12] The quaternary benzophenanthridine alkaloids which favor the iminium ion in the iminium ion ⇄ alkanolamine equilibrium in 50% aqueous ethanol solution have been found to possess higher antitumor activity, while those that favor the alkanolamine show higher cytotoxicities and antimicrobial activities.[13] Nitidine (1) lacks mutagenicity[14] and is inactive against a strain of P388 leukemia that was resistant to adriamycin.[15]

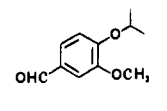
The potential therapeutic utility of nitidine (1) and fagaronine (2) is severely limited by their acute toxicity and rather narrow spectrum of antitumor activity. Research has therefore been directed toward the preparation and testing of structural analogues of these natural products in an effort to obtain compounds that might have a more favorable therapeutic index and might also possess activity against solid tumors.[8b,9,16] We recently reported the synthesis and antitumor evaluation of an indenoisoquinoline analogue 3 of nitidine (1).[17] Analogue 3 pos-



3, $R^1 + R^2 = CH_2$
4, $R^1 = H$; $R^2 = CH_3$
16, $R^1 = SO_2CH_3$; $R^2 = CH_3$

sessed higher activity (optimal T/C = 198) in the L1210 screen than that reported for the natural product 1 itself (optimal T/C = 136),[8b] and it also exhibited activity against M5076 sarcoma (optimal T/C = 137 (Table I)), while nitidine (1) is inactive (optimal T/C = 91) in this system.[18] These encouraging results stimulated the synthesis and biological evaluation of the corresponding indenoisoquinoline analogue 4 of fagaronine (2) as described in the present report.

Chemistry. The Schiff base 6, derived from 4-isopropoxy-3-methoxybenzaldehyde (5) and methylamine, condensed with 4,5-dimethoxyhomophthalic anhydride (7) in chloroform at room temperature to yield a mixture of cis (J_{AB} = 6 Hz) and trans (J_{AB} = 0 Hz) diastereomeric isoquinolones 8 and 9, respectively.[20] The major cis isomer 8 selectively precipitated from the reaction mixture in 65% yield.



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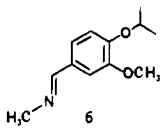

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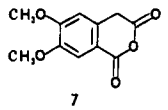

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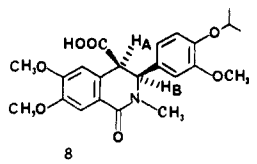

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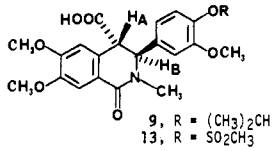
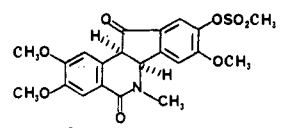


9, R = $(CH_3)_2CH$
13, R = SO_2CH_3

A reagent prepared from phosphorus pentoxide and methanesulfonic acid[21] was utilized at 50–60 °C to convert the product 8 to a mixture from which the intramolecular Friedel–Crafts reaction product 10 (68%) in which the



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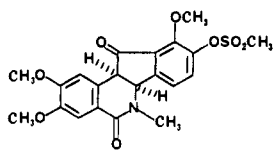

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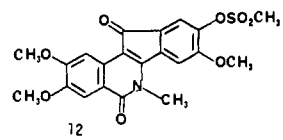

12

isopropyl protecting group was exchanged for a methanesulfonyl protecting group, the positional isomer 11 (7%), and a small amount of a dehydrogenated compound 12 (0.003%) were isolated. Compound 11 was readily distinguished from its isomer 10 by the AB coupling pattern (J = 8 Hz) for the ortho aromatic hydrogens, which were evident in its NMR spectrum. The novel protecting group exchange undoubtedly results from acidic cleavage of the isopropyl ether[22] followed by reaction of the phenol with either a mixed anhydride[21] or methanesulfonic anhydride[23] present in the reaction mixture. Alternative efforts to cyclize intermediate 8 with phosphorus pentoxide itself or with polyphosphoric acid under a variety of reaction conditions always led to disappointing results, presumably due to cleavage of the isopropyl group followed

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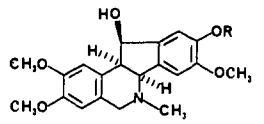
by intermolecular esterification. Subjection of the minor trans diastereomer **9** to the phosphorus pentoxide–methanesulfonic acid reagent gave the desired epimerized cis-fused isoquinoline **10** (42%) along with the mesylated trans acid **13** (44%).

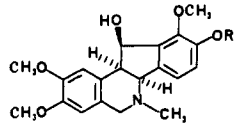
Attempted lithium aluminum hydride reduction of the keto lactam **10** to the amino alcohol **14** led to the recovery



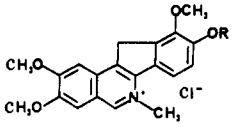
14, R = SO_2CH_3
15, R = H

of starting material. The sluggishness of lithium aluminum hydride reductions in the presence of sulfonyl groups has already been noted.[24] In order to circumvent this difficulty, the reduction was performed with diborane,[25] which smoothly produced the desired intermediate **14** in 80% yield. The relative configuration of the carbinol carbon of **14** is dictated by the approach of the reagent to the more accessible convex face of the intermediate **10**. Saponification of the methanesulfonate group of **14** with alcoholic potassium hydroxide quantitatively afforded the phenol **15**, which underwent dehydration as well as dehydrogenation in the presence of palladium on charcoal in refluxing acetic acid. The target molecule **4** was isolated in 65% yield as the chloride salt. The corresponding mesylate derivative **16** was also prepared by a similar dehydration and dehydrogenation of intermediate **14**.

Although it is well-known that changing from an 8,9-substitution to a 7,8-substitution pattern in ring D of the quaternary benzophenanthridines abolishes antitumor activity,[13,26] less information is available concerning the effect of altering the substitution pattern of the A ring. The conversion of the minor indenoisoquinoline isomer **11** resulting from the intramolecular Friedel–Crafts cyclization of **8** to a quaternary system similar to compound **3** was therefore contemplated. Following the sequence of reactions established for the synthesis of **4**, diborane reduction of compound **11** gave the amino alcohol **17**, which was hydrolyzed to the phenol **18**. Subjection of **17** and **18** to palladium on charcoal in refluxing acetic acid yielded the quaternary salts **19** and **20**.

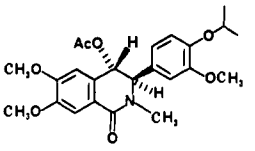


17, R = SO_2CH_3
18, R = H



19, R = SO_2CH_3
20, R = H

In order to further delineate the structural parameters associated with the antitumor activity of nitidine (**1**) and fagaronine (**2**), the minor condensation product **9** was utilized for the preparation of a tricyclic anglogue **24**. Oxidative decarboxylation of intermediate **9** with lead tetraacetate and cupric acetate in pyridine–benzene gave the acetate **21** (49%) and the alkene **22** (5%). Lithium aluminum hydride reduction of compound **21** afforded the amino alcohol **23**, which was dehydrated and dehydrogenated with palladium on charcoal in refluxing acetic acid to yield the desired analogue **24**.



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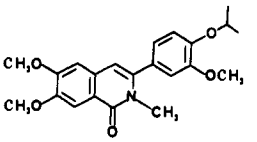

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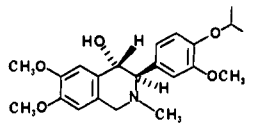

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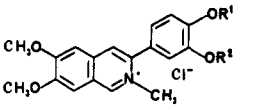

24, $R^1 = (CH_3)_2CH$; $R^2 = CH_3$
25, $R^1 + R^2 = CH_2$

In agreement with the general observation that the quaternary benzophenanthridine alkaloids tend to bear undefined contents of water of crystallization,[27] compounds **4**, **16**, **19**, **20**, and **24** were all isolated as hydrates containing from one to two molecules of water.

Biological Results and Discussion. The cytotoxicities of the quaternary compounds as well as the keto lactam **10** were determined in the KB cancer cell culture system, and the ED_{50} values are listed in Table II. All of these compounds proved to be cytotoxic with the notable exception of the tricyclic system **24**. The lack of activity of **24** sharply contrasts with the closely related analogue **25** of nitidine, which displayed significant cytotoxicity (ED_{50} = 0.005 μg/mL) in the in vitro KB cell culture system.

Analogues **4**, **16**, and **20** were also tested in vivo in the P388 mouse leukemia screen. The results are shown in Table III. Each of these substances displayed approxi-

Table II. In Vitro KB Cytotoxicities of Certain Fagaronine Analogues[a]

compd	ED_{50}, μg/mL	compd	ED_{50}, μg/mL
4	0.03	**19**	0.1
10	0.5	**20**	0.4
16	0.01	**24**	>100

[a] The KB cell line, derived from a human epiermoid carcinoma,[28] was originally supplied by Arthur D. Little, Inc., and the cell culture screen was performed according to standard protocol.[29] The ED_{50} values were obtained by extrapolation from a least-squares fit of the dose–response curve.

Table III. Evaluation of Compounds **4**, **16**, and **20** for Anticancer Activity against P388 Leukemia

compd	dose, mg/kg	survival	wt diff	% T/C
4	50	6/6	−0.4	149
	25	6/6	−0.1	138
	12.5	5/5	0.1	130
16	200	5/6	−3.6	145
	100	6/6	−2.1	137
	50	6/6	−0.6	136
	25	6/6	−1.3	128
20	400	6/6	−1.5	137
	200	6/6	−0.2	134
	100	6/6	0.2	116

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mately equal antitumor activity as judged by the optimal T/C values, which are lower than that reported for fagaronine chloride itself (optimal T/C = 265) against P388 lymphocytic leukemia.[3] The A-ring of these compounds therefore does appear to tolerate a change in the substitution pattern without a significant decrease in antitumor activity, although the potency is somewhat depressed on going from compound **4** to its positional isomer **20**.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or on a Meltemp 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 accumulated by using 32 K 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 2-methylpropane or methane as the reagent gas. Organic extracts were dried by using Na_2SO_4.

4-Isopropoxy-3-methoxybenzaldehyde (5). Isopropyl bromide (75 mL, 0.80 mol) and anhydrous potassium carbonate (75 g) were added to a mixture of vanillin (25 g, 0.16 mol) and DMF (50 mL). The mixture was heated at reflux for 2.5 h, cooled, and poured into water. On standing, a heavy liquid separated out and was extracted with chloroform (4 × 50 mL). The chloroform layer was thoroughly washed with water (6 × 50 mL) to remove the DMF and then dried. The chloroform extract was then concentrated to yield a pale yellow liquid (27.68 g, 86%). The liquid was distilled under high vacuum to yield a pale yellow liquid: bp 117–120 °C (0.4 mm) [lit.[30] bp 150–152 °C (13 mm)]; IR (neat) 2960, 2800, 1670, 1580, 1260, 1100 cm^{-1}; NMR δ 9.69 (s, 1 H), 7.35–7.24 (m, 2 H), 6.82 (d, 1 H, J = 8.7 Hz), 4.54 (hept, 1 H, J = 6.1 Hz), 3.75 (s, 3 H), 1.26 (d, 6 H, J = 6.1 Hz).

4-Isopropoxy-3-methoxybenzylidenemethylamine (6). 4-Isopropoxy-3-methoxybenzaldehyde (**5**; 7 g, 0.036 mol) and a saturated aqueous solution of methylamine (7 mL) were stirred at room temperature in absolute ethanol (10 mL) for 6 h. The reaction mixture was diluted with absolute ethanol (50 mL), dried over molecular sieves (4A), and filtered. The liquid was concentrated and more absolute ethanol (20 mL) added. The solution was again concentrated to yield a yellow liquid (6 g, 80%). The liquid was distilled by evaporative distillation: bp 125–126 °C (0.2 mm); IR (neat) 2940, 1630, 1250, 1215, 1120 cm^{-1}; NMR δ 8.16 (d, 1 H, J = 1.5 Hz), 7.37 (d, 1 H, J = 1.8 Hz), 7.09 (d of d, 1 H, J = 8.2, 1.8 Hz), 6.85 (d, 1 H, J = 8.2 Hz), 4.57 (hept, 1 H, J = 6.1 Hz), 3.88 (s, 3 H), 3.46 (d, 3 H, J = 1.5 Hz), 1.36 (d, 6 H, J = 6.1 Hz).

***cis*- and *trans*-*N*-Methyl-3-(4-isopropoxy-3-methoxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (8 and 9).** 4,5-Dimethoxyhomophthalic anhydride[31] (**7**; 0.53 g, 2.4 mmol) was added in one portion to a stirred solution of 4-isopropoxy-3-methoxybenzylidenemethylamine (**6**; 5 g, 2.4 mmol) in $CHCl_3$ (20 mL). After the mixture was stirred at room temperature for 30 min, the precipitate was filtered and washed with chloroform (10 mL) to give the cis acid **8** as a white solid (0.66 g, 65%): mp 222–224 °C; IR (KBr) 3400, 2920, 1730, 1610, 1590, 1270, 1250, 1210 cm^{-1}; NMR ($CDCl_3$ + pyridine-d_5) δ 8.83 (br s, 1 H, exchangeable with D_2O), 8.03 (d, 1 H, J = 9.6 Hz), 6.90 (s, 1 H), 6.84 (d, 1 H, J = 9.8 Hz), 6.80 (s, 1 H), 6.73 (s, 1 H), 5.19 (d, 1 H, J = 6.4 Hz), 4.79 (d, 1 H, J = 6.4 Hz), 4.33 (hept, 1 H, J = 6.1 Hz), 3.84 (s, 3 H), 3.73 (s, 3 H), 3.48 (s, 3 H), 3.14 (s, 3 H), 1.19 (d, 6 H, J = 6.0 Hz); CIMS, m/e (relative intensity) 430 (M^+ + 1, 70), 414 (37), 386 (100), 370 (13), 344 (30). Anal. ($C_{23}H_{27}NO_7$) C, H, N.

The filtrate was evaporated to yield a yellow solid (0.35 g, 35%). Recrystallization from benzene by triturating with hexane gave the trans acid **9** as a white powder: mp 125–127 °C; IR (KBr) 2900, 1710, 1605, 1580, 1555, 1490, 1235 cm^{-1}; NMR δ 7.64 (s, 1 H), 7.34 (s, 1 H), 6.67–6.55 (m, 3 H), 5.69 (br s, 1 H, exchangeable with D_2O), 5.06 (s, 1 H), 4.43 (hept, 1 H, J = 6.1 Hz), 3.91 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 1 H), 3.69 (s, 3 H), 3.09 (s, 3 H), 1.30 (d, 6 H, J = 6.1 Hz); CIMS, m/e (relative intensity) 430 (M^+ + 1, 100), 412 (31), 388 (35), 264 (12). Anal. ($C_{23}H_{27}NO_7$) C, H, N.

***cis*-2,3,8-Trimethoxy-5,6,12,13-tetrahydro-5,11-diketo-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno[1,2-*c*]isoquinoline (10) and *cis*-2,3,10-Trimethoxy-5,6,12,13-tetrahydro-5,11-diketo-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno[1,2-*c*]isoquinoline (11).** The cis acid **8** (0.8 g, 1.86 mmol) was added to a freshly prepared solution of methanesulfonic acid (25 g) and phosphorus pentoxide (2.5 g) at 40 °C. The solution was stirred for 2 h at 50–60 °C. After cooling, the reaction was quenched by slowly adding water (60 mL) and stirring at room temperature for 45 min, when crystals precipitated out of solution. The aqueous mixture was extracted with chloroform (3 × 30 mL), and the chloroform extract was washed with 5% sodium bicarbonate solution (3 × 20 mL) and water (2 × 30 mL). After drying of the chloroform layer, it was filtered and evaporated to dryness to yield product (0.8 g). Recrystallization from a chloroform solution by slow addition of methanol produced the keto amide **10** as shiny white prisms (0.57 g, 68%): mp 244–245 °C (dec); IR (KBr) 1700, 1635, 1585, 1475, 1350, 1280 1250 cm^{-1}; NMR δ 7.65 (s, 1 H), 7.58 (s, 1 H), 7.16 (s, 2 H), 5.18 (d, 1 H, J = 7.2 Hz), 4.66 (d, 1 H, J = 7.2 Hz), 3.99 (s, 3 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.50 (s, 3 H), 3.19 (s, 3 H); CIMS, m/e (relative intensity) 449 (21), 448 (M^+ +1, 100), 371 (29), 369 (4). Anal. ($C_{21}H_{21}NO_8S$) C, H, N, S.

A similar experiment, run on a large scale (32 g of the cis acid **8**), gave on recrystallization a first crop of the keto amide **10** as white prisms (16.08 g, 48%). The second crop of crystals (5 g, 15%) was shown by TLC to be a mixture and was subjected to column chromatography on silica gel (ethyl acetate as eluent). The second group of fractions (R_f 0.33, silica gel, ethyl acetate) gave the keto amide **11** as a red residue (2.3 g, 7%). An analytical sample was prepared by recrystallization from $CHCl_3$–MeOH to yield prisms: mp 242–244 °C; IR (KBr) 1705, 1645, 1590, 1470, 1340, 1260, 1155 cm^{-1}; NMR (200 MHz) δ 7.61 (s, 1 H), 7.59 (d, 1 H, J = 8.4 Hz), 7.39 (d, 1 H, J = 8.3 Hz), 7.06 (s, 1 H), 5.18 (d, 1 H, J = 8.2 Hz), 4.26 (d, 1 H, J = 8.0 Hz), 4.05 (s, 3 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 3.49 (s, 3 H), 3.20 (s, 3 H); CIMS, m/e (relative intensity) 448 (M^+ + 1, 41), 370 (26), 81 (100). Anal. ($C_{21}H_{21}NO_8S \cdot 0.5H_2O$) C, H, N, S.

The third group of fractions (R_f 0.09, silica gel, ethyl acetate) gave additional keto amide **10** (1.9 g, 6%), mp 244–245 °C (dec).

2,3,8-Trimethoxy-5,6-dihydro-5,11-diketo-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno[1,2-*c*]isoquinoline (12). The first group of fractions (R_f 0.65, silica gel, ethyl acetate) from the column above gave the keto amide **12** as a red product (81 mg, 0.002%): mp 248–250 °C; IR (KBr) 1780, 1650, 1580, 1470, 1360, 1295 cm^{-1}; NMR (200 MHz) δ 8.08 (s, 1 H), 7.67 (s, 1 H), 7.40 (d, 1 H, J = 8.1 Hz), 7.33 (d, 1 H, J = 8.1 Hz), 4.16 (s, 3 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.99 (s, 6 H); CIMS, m/e (relative intensity) 447 (4), 446 (M^+ + 1, 30), 369 (11), 368 (81), 89 (16), 81 (100). Anal. ($C_{21}H_{19}NO_8S \cdot H_2O$) C, H, N, S.

***trans*-*N*-Methyl-3-(4-[(methylsulfonyl)oxy]-3-methoxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (13).** The trans acid **9** (50 mg, 0.12 mmol) was added to a freshly prepared solution of methanesulfonic acid (1.6 g) and phosphorus pentoxide (0.15 g). After heating at 60–70 °C for 21 h, the reaction mixture was cooled and slowly quenched with water (5 mL). After the mixture was stirred for 10 min, the aqueous layer was extracted with chloroform (3 × 10 mL). The combined chloroform layers were washed with 5% sodium bicarbonate solution (2 × 15 mL) and water (10 mL). After drying, the chloroform layer was evaporated to dryness to yield a product (22 mg, 42%) that was characterized as the already obtained mesylated keto amide **10**.

The bicarbonate wash was acidified with concentrated hydrochloric acid (pH 2) and extracted with chloroform (2 × 15 mL).

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The combined chloroform layers were washed with water (20 mL), dried, and evaporated to dryness to give white crystals (27 mg, 44%): mp 147–149 °C; IR (KBr) 3400, 2920, 1715, 1590, 1495, 1350, 1100, 1010 cm^{-1}; NMR (200 MHz) δ 7.64 (s, 1 H), 7.18 (d, 1 H, J = 8.3 Hz), 6.68 (d of d, 1 H, J = 8.2, 2.0 Hz), 6.63 (s, 2 H), 5.14 (s, 1 H), 4.39 (br s, 1 H, exchangeable with D_2O), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 1 H), 3.73 (s, 3 H), 3.16 (s, 3 H), 3.12 (s, 3 H); CIMS, m/e (relative intensity) 467 (22); 466 (M^+ + 1, 100), 422 (35), 388 (16), 344 (35).

***cis*-2,3,8-Trimethoxy-5,6,12α,13α-tetrahydro-11β-hydroxy-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno-[1,2-*c*]isoquinoline (14).** The mesylated keto amide **10** (300 mg, 0.66 mmol) was heated at reflux for 4 h with a solution prepared by dissolving 1 M BH_3 in THF (3.25 mL, 3.25 mmol) in freshly dried and distilled THF (50 mL). After the reaction mixture was cooled in ice, it was slowly quenched with 3 N HCl (0.6 mL) and concentrated to ca. 15 mL. When more THF was evaporated, white crystals were observed to precipitate from the solution. Crystallization was completed by slow trituration with water and storage in a refrigerator for 2 h. The product was filtered, washed with water, and dried overnight over P_2O_5 under vacuum to yield a white powder (262 mg, 80%): mp 195–197 °C (dec); IR (KBr) 3235, 2175, 1345, 1155, 1070 cm^{-1}; NMR (470 MHz) δ 7.94 (s, 1 H), 7.44 (s, 1 H), 6.76 (s, 1 H), 6.64 (s, 1 H), 5.37 (d, 1 H, J = 6.4 Hz), 4.75 (d, 1 H, J = 8.2 Hz), 4.44 (d, 1 H, J = 16 Hz), 3.98 (s, 3 H), 3.95 (d, 1 H, J = 13.3 Hz), 3.93 (s, 3 H), 3.89 (s, 3 H), 3.67 (t, 1 H, J = 7.3 Hz), 3.23 (s, 3 H), 2.19 (s, 3 H); CIMS, m/e (relative intensity) 436 (M^+ + 1, 8), 418 (7), 372 (5), 354 (11), 340 (5), 236 (13), 178 (7), 148 (5), 81 (100). Anal. ($C_{21}H_{25}NO_7S·3H_2O$) C, H, N, S.

***cis*-2,3,8-Trimethoxy-5,6,12α,13α-tetrahydro-11β-hydroxy-6-methyl-9-hydroxy-11*H*-indeno[1,2-*c*]isoquinoline (15).** The mesylated amino alcohol **14** (113 mg, 0.26 mmol), potassium hydroxide (100 mg, 1.79 mmol), water (sufficient to dissolve the KOH), and absolute ethanol (16 mL) were heated at reflux for 1 h. The solution usually assumed a transparent light green color. After the solvent was evaporated, the residue was dissolved in water (20 mL) and washed with chloroform (5 mL). The aqueous solution was acidified with concentrated hydrochloric acid (pH 2) and made basic with solid sodium bicarbonate (pH 8). The aqueous layer was extracted with chloroform (3 × 15 mL). The combined pink chloroform layers were washed with water (20 mL), dried, filtered, and evaporated to yield a residue (82 mg, 100%). An analytical sample was prepared by preparative TLC (silica, 40% ethyl acetate in chloroform as eluent): mp 208–209 °C; IR (KBr) 3400, 3200, 2920, 1450, 1315, 1240, 1080 cm^{-1}; NMR (470 MHz) δ 7.12 (s, 1 H), 6.90 (s, 1 H), 6.81 (s, 1 H), 6.61 (s, 1 H), 5.71 (br s, 2 H), 4.91 (d, 1 H, J = 5.0 Hz), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.84 (d, 1 H, J = 15.0 Hz), 3.50 (d, 1 H, J = 14.7 Hz), 3.43 (d, 1 H, J = 4.2 Hz), 3.37 (d of d, 1 H, J = 4.6, 4.5 Hz), 2.37 (s, 3 H); CIMS, m/e (relative intensity) 359 (15), 358 (M^+ + 1, 100), 341 (10), 340 (56). CIMS, m/e 358.1654 (M^+ + 1); calcd for $C_{20}H_{23}NO_5$ 358.1641.

2,3,8-Trimethoxy-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno[1,2-*c*]isoquinolinium Chloride (16). The mesylated amino alcohol **14** (92 mg, 0.21 mmol) was heated at reflux with 5% palladium on charcoal (50 mg) and glacial acetic acid (25 mL) for 24 h. After the reaction mixture was filtered through Celite, the acetic acid was evaporated to yield a yellowish brown residue that was dissolved in water (2 mL) and ethanol (0.5 mL). Aqueous sodium chloride (1 mL, 15%) was added to this solution, which was then refrigerated for 2 h to effect crystallization. The product was filtered and washed with a minimum quantity of water and dried over P_2O_5 under vacuum overnight to yield a yellow product (81 mg, 76%). An analytical sample was prepared by recrystallization from absolute ethanol to give a white powder: mp 212–214 °C (dec); IR (KBr) 3350, 1600, 1480, 1335, 1220, 1150, 1090, 1000 cm^{-1}; NMR (Me_2SO-d_6) δ 9.60 (s, 1 H), 7.89 (s, 1 H), 7.81 (s, 1 H), 7.76 (s, 1 H), 7.65 (s, 1 H), 4.82 (s, 2 H), 4.44 (s, 3 H, exchangeable with D_2O), 4.14 (s, 3 H), 4.07 (s, 3 H), 4.02 (s, 3 H), 3.49 (s, 3 H), 3.31 (s, 3 H). Anal. ($C_{21}H_{22}NClO_6S·1.5H_2O$) C, H, N, Cl, S.

2,3,8-Trimethoxy-6-methyl-9-hydroxy-11*H*-indeno[1,2-*c*]isoquinolinium Chloride (4). The phenolic amino alcohol **15** (1.8 g, 5.04 mmol) was heated at reflux with 5% palladium on charcoal (0.9 g) and glacial acetic acid (125 mL) for 24 h. The reaction mixture was filtered through Celite and the acetic acid evaporated. The residue was dissolved in water (10 mL), and to the solution was added 15% aqueous sodium chloride (4.5 mL) and acetone (5 mL). Crystallization was effected by keeping in a refrigerator for 0.5 h. More water (5 mL) was added, and the crystals were kept in the refrigerator for another 1 h after which they were filtered. The product was washed with a minimum amount of acetone–water mixture (50:50) followed by neat acetone. The product was dried over P_2O_5 under vacuum overnight to yield fine brown needles (1.12 g, 55%): mp 232–234 °C (dec); IR (KBr) 3400, 1600, 1485, 1310, 1220, 1000 cm^{-1}; NMR (Me_2SO-d_6) δ 10.03 (s, 1 H, exchangeable with D_2O), 9.40 (s, 1 H), 7.68 (s, 1 H), 7.65 (s, 1 H), 7.53 (s, 1 H), 7.27 (s, 1 H), 4.72 (s, 3 H), 4.31 (s, 2 H), 4.11 (s, 3 H), 3.99 (s, 3 H), 3.96 (s, 3 H). Anal. ($C_{20}H_{20}NO_4Cl·1.5H_2O$) C, H, N, Cl.

***cis*-2,3,10-Trimethoxy-5,6,12α,13α-tetrahydro-11β-hydroxy-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno-[1,2-*c*]isoquinoline (17).** The mesylated keto amide **11** (0.7 g, 1.57 mmol) was heated at reflux for 4 h with a solution prepared by dissolving 1 M BH_3 in THF (8 mL, 8 mmol) in freshly dried and distilled THF (40 mL). After the mixture was stirred at room temperature for 2 h, it was quenched by slowly adding 3 N HCl (1.6 mL) and further stirred for 2 h. The solution was concentrated by evaporation to ca. 10 mL followed by slow addition of water (20 mL), when a white product precipitated from solution. The mixture was refrigerated for 1 h, filtered, washed with water, and dried over P_2O_5 under vacuum overnight to yield an offensive smelling white powder. A second crop yielded additional product. The yield was 0.67 g, 91%: mp 250–252 °C (dec); IR (KBr) 3460, 1600, 1505, 1480, 1340, 1240, 1160, 1070 cm^{-1}; NMR δ 8.06 (d, 1 H, J = 9 Hz), 7.39 (d, 1 H, J = 9 Hz), 6.78 (s, 1 H), 6.65 (s, 1 H), 5.68 (d, 1 H, J = 7 Hz), 4.76 (d, 1 H, J = 8 Hz), 4.46 (d, 1 H, J = 16 Hz), 4.07 (s, 4 H), 3.94 (s, 3 H), 3.89 (s, 3 H), 3.82 (m, 1 H), 3.24 (s, 3 H), 2.21 (s, 3 H); CIMS, m/e (relative intensity) 436 (M^+ + 1, 21), 420 (100), 418 (23), 405 (8), 81 (17). Anal. ($C_{21}H_{25}NO_7S·2.5H_2O$) C, H, N, S.

***cis*-2,3,10-Trimethoxy-5,6,12α,13α-tetrahydro-11β-hydroxy-6-methyl-9-hydroxy-11*H*-indeno[1,2-*c*]isoquinoline (18).** The mesylated amino alcohol **17** (0.88 g, 2.02 mmol) was heated at reflux with potassium hydroxide (0.88 g, 15.71 mmol), water (few drops sufficient to dissolve the KOH), and absolute ethanol (100 mL) for 2 h. After the solvent was evaporated, water (10 mL) was added and the aqueous solution washed with chloroform (3 × 40 mL). The aqueous layer was acidified with concentrated hydrochloric acid (pH 2) and made basic with solid sodium bicarbonate (pH 8). The aqueous fraction was extracted with chloroform (3 × 40 mL) and combined with the chloroform layers obtained from the wash. The combined organic fraction was washed with water (2 × 40 mL), dried, filtered, and evaporated to dryness to yield a pale pink residue (0.62 g, 95%): mp 258–262 °C (dec). The product, without further purification, was carried onto the final step; CIMS, m/e (relative intensity) 359 (19), 358 (M^+ + 1, 100), 341 (6), 340 (30).

2,3,10-Trimethoxy-6-methyl-9-[(methylsulfonyl)oxy]-11*H*-indeno[1,2-*c*]isoquinolinium Chloride (19). The mesylated amino alcohol **17** (600 mg, 1.38 mmol) was heated at reflux with 5% palladium on charcoal (300 mg) and glacial acetic acid (120 mL) for 24 h. The reaction mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was dissolved in water (4.3 mL), and to the solution was added 15% aqueous sodium chloride (4.7 mL). Turbidity was observed after keeping in a refrigerator for 30 min. Scratching induced crystallization. After further cooling for 2 h, the crystals were filtered and dried over P_2O_5 under vacuum overnight to yield a yellowish brown powder. The filtrate yielded two more crops of additional product. The yield was 370.1 mg, 63%: mp >330 °C (dec); IR (KBr) 3350, 1600, 1480, 1410, 1200, 1155, 1010 cm^{-1}; NMR (Me_2SO-d_6) δ 9.56 (s, 1 H), 8.20–7.67 (m, 4 H), 4.73 (s, 2 H), 4.60 (s, 3 H), 4.14 (s, 6 H), 4.02 (s, 3 H), 3.57 (s, 3 H); FABMS, m/e (relative intensity) 416 (M^+ – Cl, 39), 337 (33), 323 (100). Anal. ($C_{21}H_{22}NClO_6S·1H_2O$) C, H, N, Cl.

2,3,10-Trimethoxy-6-methyl-9-hydroxy-11*H*-indeno[1,2-*c*]isoquinolinium Chloride (20). The phenolic amino alcohol 18 (0.8 g, 2.24 mmol) was heated at reflux with 5% palladium on charcoal (0.4 g) and glacial acetic acid (65 mL) for 24 h. The reaction mixture was filtered through Celite and the acetic acid

evaporated to leave an oily residue that dissolved in water (6 mL). Aqueous sodium chloride (2 mL, 15%) and acetone (4 drops) were added to the solution. Precipitation occurred almost immediately. The flask was cooled in the refrigerator for 1 h, and the product was filtered and washed with a minimum amount of acetone–water (50:50) and acetone. The product was dried over P_2O_5 under vacuum overnight to yield a pale yellowish brown powder (0.48 g, 52%): mp 242–244 °C (dec); IR (KBr) 3400, 1600, 1485, 1310, 1215, 1200, 1000 cm^{-1}; NMR (Me_2SO-d_6) δ 10.36 (s, 1 H), 9.43 (s, 1 H), 7.84 (d, 1 H, J = 8.5 Hz), 7.68 (s, 2 H), 7.14 (d, 1 H, J = 8.5 Hz), 4.64 (s, 3 H), 4.41 (s, 2 H), 4.14 (s, 3 H), 4.00 (s, 3 H), 3.96 (s, 3 H). Anal. ($C_{20}H_{20}NO_4Cl \cdot 2H_2O$) C, H, N, Cl.

***trans*-*N*-Methyl-3-(4-isopropoxy-3-methoxyphenyl)-4-acetoxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (21).** The trans acid **9** (1 g, 2.4 mmol), lead tetracetate (1.04 g, 1.2 mmol), and cupric acetate (20 mg, 0.12 mmol) were added to dry benzene (75 mL) and dry pyridine (1 mL). The mixture was purged with nitrogen for 3 h and then heated at 80 °C for 3 h. After overnight stirring at room temperature, the reaction mixture was filtered and the precipitate washed with benzene. The benzene layer was successively washed with water (2 × 40 mL), 5% sodium bicarbonate solution (2 × 40 mL), and water (2 × 40 mL). The benzene layer was dried, filtered, and evaporated to dryness to yield a solid product that was subjected to column chromatography on silica gel (ethyl acetate as eluent) to yield a thick oil that solidified on addition of carbon tetrachloride and hexane to give white crystals (0.56 g, 49%): mp 139–140 °C; IR (KBr) 2600, 1730, 1640, 1590, 1500, 1210, 1010 cm^{-1}; NMR δ 7.60 (s, 1 H), 6.67–6.44 (m, 4 H), 5.70 (d, 1 H, J = 1.6 Hz), 4.63 (d, 1 H, J = 1.3 Hz), 4.31 (hept, 1 H, J = 6.1 Hz), 3.83 (s, 3 H), 3.71 (s, 3 H), 3.60 (s, 3 H), 3.01 (s, 3 H), 1.95 (s, 3 H), 1.17 (d, 6 H, J = 6.0 Hz); CIMS, m/e (relative intensity) 444 ($M^+ + 1$, 40), 384 (100), 342 (30). Anal. ($C_{24}H_{29}NO_7 \cdot 1.5H_2O$) C, H, N.

***N*-Methyl-3-(4-isopropoxy-3-methoxyphenyl)-6,7-dimethoxy-1(2*H*)-isoquinolone (22).** Further column chromatography on silica gel (ethyl acetate as eluent) of the above reaction product gave a second group of pure fractions that on evaporation yielded white crystals (45 mg, 5%), mp 189–191 °C. Recrystallization from benzene–hexane gave white prisms: mp 192–194 °C; IR (KBr) 1635, 1585, 1495, 1240, 1025 cm^{-1}; NMR δ 7.75 (s, 1 H), 6.87–6.83 (m, 3 H), 6.77 (s, 1 H), 6.32 (s, 1 H), 4.54 (hept, 1 H, J = 6.1 Hz), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.38 (s, 3 H), 1.35 (d, 6 H, J = 6.1 Hz). Anal. ($C_{22}H_{25}NO_5$) C, H, N.

***trans*-*N*-Methyl-3-(4-isopropoxy-3-methoxyphenyl)-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (23).** The amide **21** (0.36 g, 0.71 mmol) was heated at reflux with lithium aluminum hydride (0.48 g, 12.6 mmol) and freshly dried and distilled THF (35 mL) for 27 h. After the mixture was cooled to room temperature, the reaction vessel was cooled in ice while it was sequentially quenched with water (0.5 mL), 15% sodium hydroxide solution (0.5 mL), and water (1.5 mL). After the reaction was stirred for 15 min, chloroform (40 mL) was added, the mixture was stirred for 45 min, filtered, and dried, and the filtrate was evaporated to yield a greenish white product (0.28 g, 98%). Recrystallization by dissolving in benzene and triturating with hexane gave white crystals (0.18 g, 62%): mp 118–120 °C; IR (KBr) 3400, 1500, 1245, 1120 cm^{-1}; NMR δ 7.02 (s, 1 H), 6.80 (m, 3 H), 6.56 (s, 1 H) 4.76 (d, 1 H, J = 6.4 Hz), 4.52 (hept, 1 H, J = 6.1 Hz), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.70 (s, 1 H), 3.66 (s, 1 H), 3.39 (d, 1 H, J = 6.4 Hz), 2.24 (s, 3 H), 2.01 (br s, 1 H, exchangeable with D_2O), 1.37 (d, 6 H, J = 6 Hz); CIMS, m/e (relative intensity) 388 ($M^+ + 1$, 78), 370 (100), 346 (78), 328 (24). Anal. ($C_{22}H_{29}NO_5 \cdot H_2O$) C, H, N.

***N*-Methyl-3-(4-isopropoxy-3-methoxyphenyl)-6,7-dimethoxyisoquinolinium Chloride (24).** The amino alcohol **23** (0.87 g, 2.15 mmol) was heated at reflux with 5% palladium on charcoal (0.6 g) and glacial acetic acid (60 mL) for 29 h. After cooling, the reaction mixture was filtered through Celite and the filtrate evaporated to dryness. The orange oil obtained was dissolved in water (5 mL), and to the solution was added 15% aqueous sodium chloride (2.5 mL). Immediate precipitation yielded a yellow product to which was added more water (ca. 5 mL). The product was filtered, washed with a minimum amount of water (ca. 3 mL), and dried under vacuum over P_2O_5 to yield a beige powder (0.58 g, 61.7%): mp 190–192 °C (dec); IR (KBr) 3400, 1490, 1405, 1200 cm^{-1}; NMR (Me_2SO-d_6) δ 9.70 (s, 1 H), 8.22 (s, 1 H), 7.77 (s, 1 H), 7.72 (s, 1 H), 7.28 (s, 1 H), 7.19 (s, 2 H), 4.71 (hept, 1 H, J = 6.1 Hz), 4.17 (s, 3 H), 4.06 (s, 3 H), 4.03 (s, 3 H) 3.81 (s, 3 H), 1.32 (d, 6 H, J = 6.0 Hz); CIMS m/e (relative intensity) 354 ($M^+ + 1 - CH_3Cl$, 100), 353 (24), 352 (9). Anal. ($C_{22}H_{26}NO_4 \cdot 2H_2O$) C, H, N, Cl.

Acknowledgment. This investigation was supported by Grant GM30932, awarded by the National Institute of General Medical Sciences, DHHS. The in vivo biological data are the results performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

Registry No. **4**, 96705-56-5; **5**, 2538-98-9; **6**, 96705-57-6; **7**, 5653-42-9; **8**, 96705-58-7; **9**, 96705-59-8; **10**, 96705-60-1; **11**, 96705-61-2; **12**, 96705-62-3; **13**, 96705-63-4; **14**, 96705-64-5; **15**, 96705-65-6; **16**, 96705-66-7; **17**, 96705-67-8; **18**, 96705-68-9; **19**, 96705-69-0; **20**, 96705-70-3; **21**, 96705-71-4; **22**, 96705-72-5; **23**, 96705-73-6; **24**, 96705-74-7; vanillin, 121-33-5; isopropyl bromide, 75-26-3.