Total Synthesis of Nitidine Chloride

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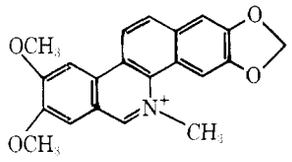
A new approach to the total synthesis of benzophenanthridine alkaloids is presented in the context of a preparation of the antileukemic agent nitidine chloride (**11**). The route proceeds from a diastereomeric mixture of isoquinolones **4** and **5** obtained in high yield by the addition of 4,5-dimethoxyhomophthalic anhydride (**2**) to 3,4-methylenedioxybenzylidenemethylamine (**3**). The pure trans isomer **5** is produced on heating the diastereomeric mixture in acetic acid. A classical Arndt–Eistert synthesis, followed by an intramolecular Friedel–Crafts acylation, affords intermediate **8**, which on $LiAlH_4$ reduction, dehydration, and dehydrogenation yields nitidine, isolated as the chloride **11**.

The benzo[*c*]phenanthridine alkaloid nitidine was first isolated from the root bark and root wood of *Zanthoxylum nitidum*, a woody climber which grows in most areas of Hong Kong.[1,2] The structure **1** of nitidine was established by its



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conversion to known compounds[2] and by synthesis of dihydronitidine.[3,4] Nitidine has since been isolated from a variety of *Zanthoxylum* and *Fagara* species in yields ranging from 0.003 to 0.07%.[5-13] Initial pharmacological testing of nitidine chloride uncovered high cytotoxicity, antileukemic activity in L1210 and P388 systems in mice, and inhibition of Lewis lung carcinoma.[14,15] However, interest in nitidine chloride as a potential chemotherapeutic agent has now waned owing to its acute toxicity.[16] Many of the reported syntheses[3,4,17] are based on the method established by Bailey and Worthing in their synthesis of chelerythrine,[18] which involves many steps and gives low overall yields. Recently we,[19] as well as Haimova et al.,[20] have been interested in synthetic applications of the condensation of Schiff bases with homophthalic anhydrides, and as a result of this work we now wish to report a new total synthesis of nitidine chloride.

The addition of 4,5-dimethoxyhomophthalic anhydride (**2**) to a solution of 3,4-methylenedioxybenzylidenemethylamine (**3**) in chloroform resulted in a rapid exothermic reaction which afforded a diastereomeric mixture of cis and trans isoquinolones **4** and **5** (Chart I). The cis isomer **4** (J_{AB} = 6 Hz) was insoluble in the reaction mixture and could be isolated in 49% yield by filtration, while the trans diastereomer **5** (J_{AB} = 0) could be isolated from the filtrate as a crystalline solid in 39% yield. On heating in refluxing acetic acid for 16 h the cis diastereomer **4** epimerized to the thermodynamically more stable trans isomer **5**. In practice, the mixture of **4** and **5** obtained by evaporation of chloroform from the reaction mixture was heated in acetic acid, which afforded the trans diastereomer **5** in 92% overall yield.

The low coupling constant (J_{AB} = 0) observed for the trans diastereomer **5** is in agreement with a preferred conformation in which the carboxyl and aromatic substituents occupy the expected pseudoaxial orientations.[19] By analogy to the effect of A strain in cyclohexenes,[21] the vicinal nonbonded interaction between the *N*-methyl substituent and the aromatic ring is expected to force the latter into the pseudoaxial conformation.

Treatment of the acid chloride of **5** with an alcohol-free ethereal solution of diazomethane gave the crystalline diazoketone **6**. Wolff rearrangement of **6** dissolved in methanol and tetrahydrofuran was performed by addition of a silver benzoate suspension in triethylamine.[22] The resulting methyl ester was hydrolyzed with potassium hydroxide in ethanol to the homologous acid **7**. Intramolecular Friedel–Crafts acylation of **7** with poly(phosphoric acid) yielded the tetracyclic ketone **8**. The conversion of **7**, in which the aromatic and carboxymethyl substituents are pseudoaxial, to the conformationally rigid tetracyclic system **8** was accompanied by a change in the NMR coupling constant between protons H_A and H_B from J_{AB} = 0 to J_{AB} = 11 Hz, thus confirming the trans disposition of protons H_A and H_B.[23] Lithium aluminum hydride reduction of **8** proceeded in 90% yield to a diastereomeric mixture of amino alcohols **9** and **10** in a 9:1 ratio as estimated by integration of the *N*-methyl signals in the NMR spectrum. The major diastereomer **9** was isolated by fractional crystallization and shown to possess the expected[24] pseudoequatorial alcohol by the appearance of the methine proton α to the alcohol as a doublet of doublets with coupling constants 5 and 12 Hz in its NMR spectrum.[23a,d] Examination of Dreiding models reveals that in the conformationally rigid system **9** a pseudoequatorial alcohol at C-12 and the 10b methine proton are trans. The minor diastereomer **10** was also isolated by fractional crystallization, and the alcohol was shown to be pseudoaxial and therefore cis to the 10b methine proton by the appearance of the methine proton α to the alcohol as an unresolved multiplet having a width at half height of 6 Hz.[23a,d] Dehydration and dehydrogenation of the diastereomeric mixture of amino alcohols **9** and **10** with palladium on charcoal in refluxing acetic acid afforded nitidine, isolated as the chloride **11** in 47% yield, accompanied by a 24% yield of the hydrogenolysis product **12**.

Experimental Section

All reactions were performed under a nitrogen atmosphere unless otherwise noted and solvents were removed on a rotary evaporator under reduced pressure. Melting points were taken on a Thomas Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument or JEOL PFT-100 spectrometer, and, except where noted, in $CDCl_3$ solvent. Chemical shifts are reported in ppm relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Dupont 21-492B double-focusing spectrometer using an ion source temperature of 200–280 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA. Microanalyses were performed by Dr. C. S. Yeh and associates of Purdue University.

***cis*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (4).** 4,5-Dimethoxyhomophthalic anhydride (**2**,[25] 2.22 g, 10 mmol) was added to a stirred solution of 3,4-methylenedioxybenzylidenemethylamine (**3**, 1.63 g, 10 mmol) in chloroform (10 mL) at 25 °C. An exothermic reaction occurred as the anhydride dissolved. After 20 min the precipitate was filtered and washed with chloroform to give a pale-yellow solid (1.88 g, 49%): mp 227–230 °C (dec). An analytical sample was obtained by recrystallization from acetic acid: mp 229–230 °C (dec);

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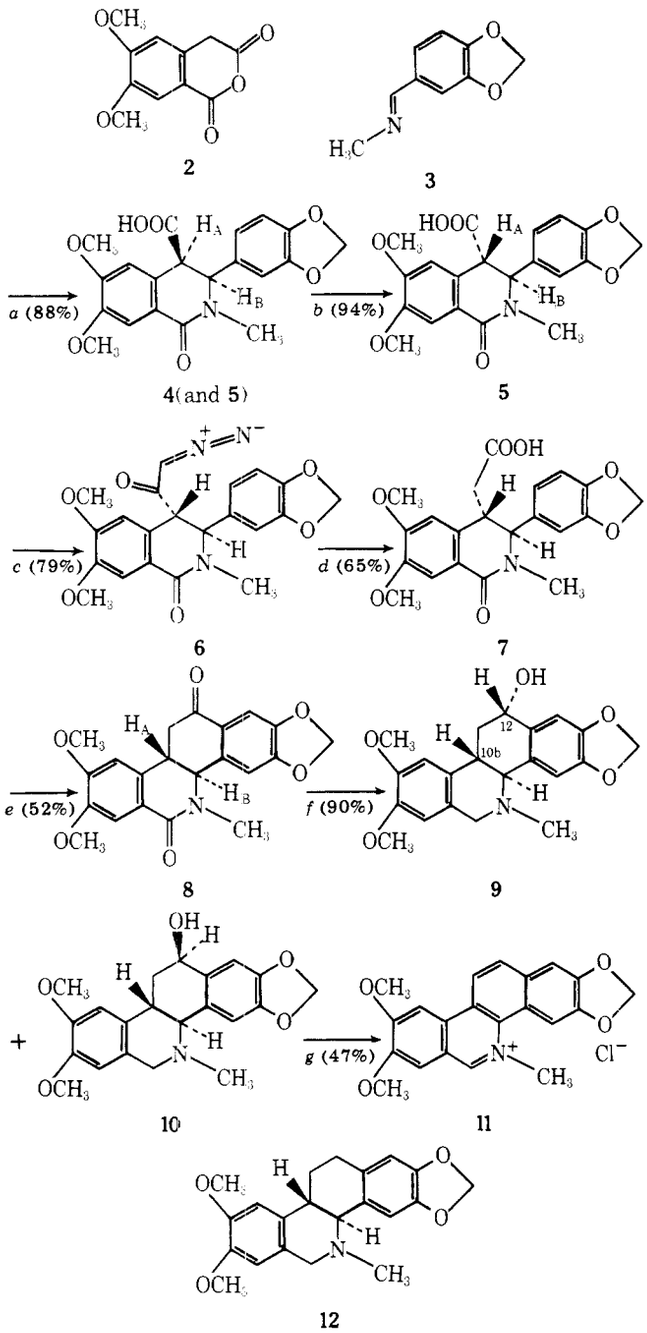
Chart I



[a] $CHCl_3$, 25 °C (30 min). [b] CH_3COOH, reflux (16 h). [c] (1) $SOCl_2$, C_6H_6, reflux (15 min), 25 °C (60 min); (2) CH_2N_2, 0 °C (5 min), then 25 °C (20 min). [d] (1) Silver benzoate, CH_3OH, THF, 25 °C (3 h); (2) KOH, 95% EtOH, reflux (1.5 h). [e] PPA, steam bath (35 min). [f] $LiAlH_4$, THF, reflux (16 h). [g] (1) CH_3COOH, 5% Pd/C, reflux (18 h); (2) aq NaCl.

IR (KBr) 3300–2800, 1740, 1625, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 8.37 (s, 1 H, exchangeable with D_2O), 7.57 (s, 1 H), 7.13 (s, 1 H), 7.00–6.50 (m, 3 H), 5.97 (s, 2 H), 5.03 (d, 1 H, J = 6 Hz), 4.63 (d, 1 H, J = 6 Hz), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.90 (s, 3 H); mass spectrum m/e (rel intensity) 385 (M^+, 17), 339 (67), 222 (53), 178 (47), 164 (100), 163 (60), 162 (73).

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.23; H, 5.12; N, 3.80.

***trans*-N-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (5).** The filtrate from the previous experiment was concentrated and the residue recrystallized from ethyl acetate to give a colorless solid (1.52 g, 39%): mp 208–209 °C; IR (KBr) 3400–2400, 1735, 1625, 1605 cm^{-1}; NMR (Me_2SO-d_6) δ 13.00 (br s, 1 H, exchangeable with D_2O), 7.50 (s, 1 H), 7.00–6.33 (m, 4 H), 5.97 (s, 2 H), 5.18 (br s, 1 H), 4.00 (s, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 2.98 (s, 3 H); mass spectrum m/e (rel intensity) 385 (M^+, 21), 341 (10), 222 (34), 194 (35), 165 (10), 164 (100), 162 (10).

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.10; H, 5.03; N, 3.47.

Epimerization of *cis*- to *trans*-N-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (5). A solution of cis acid **4** (3.00 g, 7.78 mmol) in glacial acetic acid (150 mL) was heated at reflux for 16 h. The acetic acid was evaporated under reduced pressure and the resulting yellow powder was triturated with hot benzene (100 mL). Filtration gave a very pale yellow solid (2.82 g, 94%): mp 208–210 °C.

In later experiments, the cis acid **4** was not isolated but epimerized immediately to the trans acid **5**. Thus, 4,5-dimethoxyhomophthalic anhydride (**2**, 26.85 g, 121 mmol) was added to a stirred solution of 3,4-methylenedioxybenzylidenemethylamine (**3**, 19.72 g, 121 mmol) in chloroform (450 mL) at 25 °C. At the end of 30 min the chloroform was removed under reduced pressure. To the residue was added glacial acetic acid (1200 mL) and the resulting mixture was heated at reflux for 16 h. Removal of acetic acid followed by trituration with benzene gave a pale-yellow solid (42.85 g, 92%): mp 206–209 °C.

***trans*-N-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-diazomethylcarbonyl-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (6).** A mixture of trans acid **5** (21.00 g, 54.5 mmol) and thionyl chloride (21 mL, 272 mmol) in benzene (150 mL) was heated at reflux for 15 min and then stirred at 25 °C for 1 h. Excess thionyl chloride and benzene were removed by distillation under reduced pressure. The resulting tan residue, dissolved in benzene (150 mL), was added to an ethereal solution of alcohol-free diazomethane (ca. 142 mmol) at 0 °C. After stirring at 25 °C for 20 min, the precipitate (17.69 g, 79%) was collected: mp 163.5 °C (dec). An analytical sample was obtained by recrystallization from hexane–ethyl acetate (1:1): mp 164 °C (dec); IR (KBr) 2120, 1650, 1610 cm^{-1}; NMR δ 7.77 (s, 1 H), 6.40–6.80 (m, 4 H), 5.93 (s, 2 H), 5.18 (d, 1 H, J = 1 Hz), 4.90 (s, 1 H), 4.00 (s, 3 H), 3.90 (s, 3 H), 3.62 (d, 1 H, J = 1 Hz), 3.07 (s, 3 H); mass spectrum m/e (rel intensity) 409 (M^+, 16), 381 (68), 340 (29), 339 (25), 190 (100), 164 (26), 162 (24).

Anal. Calcd for $C_{21}H_{19}N_3O_6$: C, 61.61; H, 4.68; N, 10.26. Found: C, 61.74; H, 4.80; N, 10.41.

***trans*-N-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxymethyl-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (7).** To a solution of diazoketone **6** (17.59 g, 43.0 mmol) in methanol (300 mL) and tetrahydrofuran (400 mL) was added a suspension of silver benzoate (2.29 g, 10 mmol) in triethylamine (60 mL) over a period of 25 min at 25 °C. Rapid gas evolution occurred after introduction of the silver benzoate–triethylamine suspension and the pink reaction mixture gradually darkened. At the end of 3 h, activated charcoal (Darco, 3 g) was added and the resulting mixture was heated on a steam bath. Hot filtration through Celite and concentration gave an orange oil. The orange oil was immediately hydrolyzed with potassium hydroxide (85%, 4.25 g, 64.5 mmol) in 95% ethanol (160 mL) at reflux for 1.5 h. Most of the ethanol was removed under reduced pressure, and water (150 mL) was added to the residue. The solution was acidified with concentrated hydrochloric acid. The aqueous phase was extracted with chloroform (150 mL) and the organic phase was backwashed with 5% aqueous sodium bicarbonate (ca. 900 mL). The combined aqueous extracts were acidified and extracted with chloroform (250 mL). The chloroform was evaporated and the residue recrystallized from methanol, yielding a pale-yellow solid (11.16 g, 65%): mp 203–206 °C. The analytical sample was prepared by recrystallization from methanol: mp 206–207 °C; IR (KBr) 3400–2800, 1725, 1635, 1610 cm^{-1}; NMR δ 10.60 (s, 1 H, exchangeable with D_2O), 7.63 (s, 1 H), 6.80–6.35 (m, 4 H), 5.83 (s, 2 H), 4.76 (s, 1 H), 3.90 (s, 3 H), 3.73 (s, 3 H), 3.60–3.23 (m, 1 H), 3.10 (s, 3 H), 2.92–2.62 (m, 2 H); mass spectrum m/e (rel intensity) 399 (M^+, 100), 340 (17), 339 (25), 208 (73), 191 (35), 164 (40).

Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.30; H, 5.46; N, 3.36.

***trans*-N-Methyl-2,3-methylenedioxy-6,12-dioxo-8,9-dimethoxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (8).** The acid **7** (3.60 g, 9 mmol) was stirred with poly(phosphoric acid) (36 g) exposed to air on a steam bath for 35 min during which time it changed from pale yellow through orange, then ruby, and finally to dark brown. The reaction mixture was hydrolyzed with water (400 mL) and extracted with chloroform (300 mL). The chloroform extract was backwashed with 5% sodium carbonate (200 mL) and then water (400 mL). After drying over anhydrous magnesium sulfate, removal of chloroform and trituration of the pale tan residue with hot methanol (30 mL) gave felt crystals (1.77 g, 52%): mp 272 °C (dec). An

analytical sample was prepared by column chromatography on silica gel (98:2 $CHCl_3/CH_3OH$ as eluent): mp 274 °C (dec); IR (KBr) 1680, 1650, 1605 cm^{-1}; NMR δ 7.73 (s, 1 H), 7.53 (s, 1 H), 7.00 (s, 1 H), 6.73 (s, 1 H), 6.13 (s, 2 H), 4.95 (d, 1 H, J = 11 Hz), 4.00 (s, 6 H), 3.70–3.20 (m, 2 H), 3.20 (s, 3 H), 2.77 (d, 1 H, J = 14 Hz); mass spectrum m/e (rel intensity) 381 (M^+, 75), 352 (12), 232 (14), 191 (34), 165 (100), 147 (18).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.34; H, 5.16; N, 3.69.

***N*-Methyl-2,3-methylenedioxy-8,9-dimethoxy-12α-hydroxy-4bβ,5,6,10bβ,11,12-hexahydrobenzo[*c*]phenanthridine (9).** A mixture of keto amide **8** (778 mg, 2.04 mmol) and lithium aluminum hydride (95%, 163 mg, 4.08 mmol) in THF (100 mL) was heated at reflux for 16 h. The reaction mixture was decomposed by addition of water (1 mL), 15% sodium hydroxide (1 mL), and water (3 mL) at 0 °C. The residue was filtered and washed with chloroform (75 mL), and the combined filtrates were dried over anhydrous magnesium sulfate. Removal of solvent and column chromatography on silica gel afforded colorless crystals (680 mg, 90%), mp 180–193 °C, which by NMR is a diastereomeric mixture as evidenced by the presence of two $N\text{-}CH_3$ peaks at δ 2.23 and 2.16 in the ratio of 1 to 9. Two recrystallizations from benzene gave a colorless soft solid (437 mg, 58%): mp 211–212 °C; IR (KBr) 3600–3100 cm^{-1}; NMR δ 7.22 (s, 1 H), 7.10 (s, 1 H), 6.90 (s, 1 H), 6.60 (s, 1 H), 5.95 (br s, 2 H), 4.90 (d of d, 1 H, J = 5, 12 Hz), 4.47 (d, 1 H, J = 16 Hz), 4.10–3.50 (m, 2 H), 3.90 (br s, 6 H), 3.27–2.50 (m, 2 H), 2.16 (s, 3 H), 2.00–1.20 (m, 2 H, one exchangeable with D_2O); mass spectrum m/e (rel intensity) 369 (M^+, 36), 351 (82), 350 (36), 338 (100), 192 (45).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.64; H, 6.26; N, 3.51.

***N*-Methyl-2,3-methylenedioxy-8,9-dimethoxy-12β-hydroxy-4bα,5,6,10bβ,11,12-hexahydrobenzo[*c*]phenanthridine (10).** The mother liquors from above were combined and evaporated to dryness, and the residue was subjected to fractional crystallization from benzene to give colorless crystals (19 mg, 2.5%): mp 193–195 °C; NMR δ 7.30 (s, 1 H), 6.90 (s, 1 H), 6.87 (s, 1 H), 6.60 (s, 1 H), 5.93 (s, 2 H), 4.87 (m, 1 H, $W_{1/2}$ = 6 Hz), 4.47 (d, 1 H, J = 16 Hz), 3.90 (s, 6 H), 3.80–2.52 (m, 4 H), 2.22 (s, 3 H), 2.13–1.50 (m, 2 H, one exchangeable with D_2O); mass spectrum m/e (rel intensity) 369 (M^+, 100), 351 (63), 338 (33), 336 (29), 320 (40), 192 (45).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.06; H, 6.43; N, 3.51.

Nitidine Chloride (11). A 9:1 mixture of amino alcohols **9** and **10** (0.52 g, 1.41 mmol) and 5% palladium on charcoal (180 mg) in glacial acetic acid (100 mL) was heated at reflux for 18 h. After cooling, the catalyst was removed by filtration through a pad of Celite. Evaporation of the yellow filtrate gave a green-yellow residue which was then dissolved in water (50 mL) and ethanol (10 mL). To the resulting yellow solution was added 10 mL of 15% sodium chloride solution. An immediate precipitation of flocculent material was observed. This was filtered, washed with water (25 mL), and dried over phosphorus pentoxide at 25 °C under vacuum. In this manner, a greenish-yellow residue (278 mg, 47%), mp 274–278 °C (dec, lit.[17] mp 275–277 °C), was obtained. The infrared spectrum (KBr) was identical with that of an authentic sample of nitidine chloride obtained from the National Cancer Institute. Recrystallization from methanol (50 mL) gave yellow needles (242 mg, 41%): mp 284–286 °C (dec), mixture mp 281–286 °C (dec). An authentic sample melted at 281–286 °C (dec): NMR (Me_2SO-d_6) δ 9.86 (s, 1 H), 8.95 (d, 1 H, J = 8 Hz), 8.40 (s, 1 H), 8.32 (s, 1 H), 8.30 (d, 1 H, J = 8 Hz), 7.92 (s, 1 H), 7.80 (s, 1 H), 6.36 (s, 2 H), 4.90 (s, 3 H), 4.24 (s, 3 H), 4.05 (s, 3 H); mass spectrum m/e (rel intensity) 333 ($M^+ - CH_3Cl - 2H_2O$, 100), 52 (18), 50 (CH_3Cl, 60).

Anal. Calcd for $C_{21}H_{18}NClO_4 \cdot 2H_2O$: C, 60.07; H, 5.28; N, 3.34; Cl, 8.46. Found: C, 59.95; H, 5.44; N, 3.14; Cl, 8.60.

***trans*-*N*-methyl-2,3-methylenedioxy-8,9-dimethoxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (12).** The filtrate from above was extracted with chloroform (75 mL), and the extracts were combined and washed once with water (100 mL). After drying over anhydrous magnesium sulfate, the chloroform was removed under reduced pressure. The residue, upon chromatography on silica gel (chloroform as eluent), gave a pale yellow solid (120 mg, 24%): mp 190–196 °C. One recrystallization from methanol afforded colorless plates: mp 198–200 °C; IR (KBr) 3100–2700, 1600, 1500, 1465 cm^{-1}; NMR δ 7.30 (s, 1 H), 6.93 (s, 1 H), 6.63 (s, 2 H), 5.93 (s, 2 H), 4.47 (d, 1 H, J = 16 Hz), 4.13–3.30 (m, 8 H), 3.30–2.37 (m, 3 H), 2.22 (s, 3 H), 2.10–1.33 (m, 2 H); mass spectrum m/e (rel intensity) 353 (M^+, 35), 352 (24), 323 (24), 322 (100), 84 (16).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.12; H, 6.51; N, 4.01.

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Registry No.—**2,** 5653-42-9; **3,** 63254-33-1; **4,** 64036-07-3; **5,** 64036-06-2; **6,** 64036-05-1; **7,** 64036-04-0; **8,** 64036-03-9; **9,** 64069-82-5; **10,** 64036-02-8; **11,** 13063-04-2; **12,** 64036-01-7; diazomethane, 334-88-3.

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