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Condensation of Imines with Homophthalic Anhydrides. A Convergent Synthesis of *cis*- and *trans*-13-Methyltetrahydroprotoberberines

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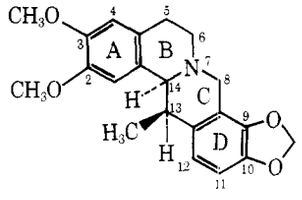
A convergent synthesis of 13-methyltetrahydroprotoberberines is presented in which the substitution pattern of ring D is dictated by that of a homophthalic anhydride precursor and the stereochemistry at C-13 is controlled by epimerization of a kinetically produced *trans*-8-oxo-13-carboxytetrahydroprotoberberine intermediate to the thermodynamically more stable cis isomer. Various aldimines and ketimines are also shown to condense with homophthalic anhydride, providing a general synthesis of 2,3-disubstituted and 2,3,3-trisubstituted 4-carboxy-3,4-dihydro-1(2*H*)-isoquinolones. The relative configurations of the diastereomers resulting from the reaction of aldimines with homophthalic anhydride are assigned on the basis of their NMR spectra in conjunction with determination of thermodynamic equilibria.

The 13-methyltetrahydroprotoberberine alkaloids constitute a small group of metabolites which occur in various species of *Corydalis*.[1] Both cis and trans diastereomers have been isolated, as exemplified by cavidine (**1**, also known as base II) and thalictrifoline (**2**), respectively.[2-4] Reported



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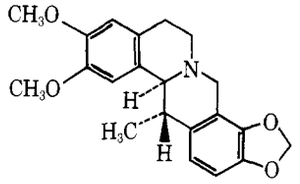

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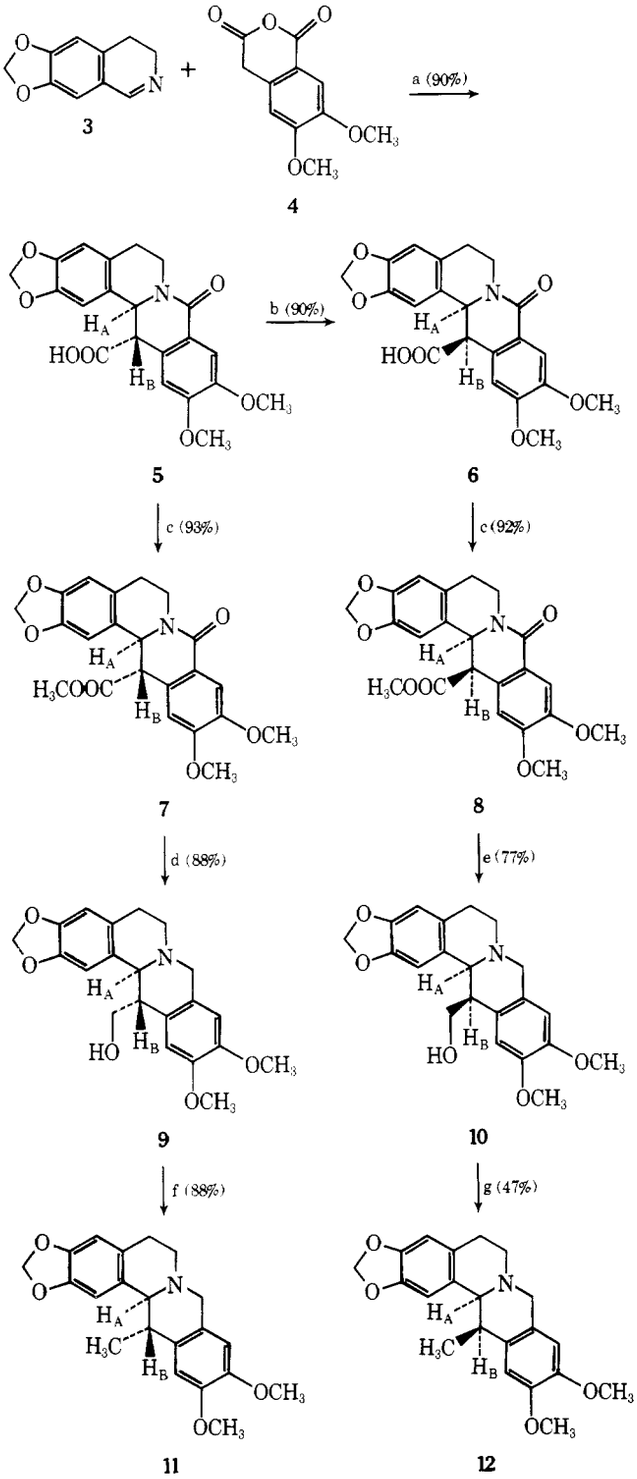
synthetic approaches to 13-methylprotoberberines include alkylation of 8-acetonyldihydroprotoberberines with methyl iodide followed by reduction,[5] which requires an intact quaternary protoberberine salt as starting material and therefore is classified as a partial synthesis; the Mannich cyclization of 1-α-methylbenzyltetrahydroisoquinolines,[6] which has been modified to allow complete stereochemical control at C-13[6c] but is not suitable for preparation of the more commonly encountered 9,10-dioxygenated protoberberines without unattractive instillation and removal of protecting groups or separation of mixtures; and the photocyclization of 1-ethylidene-2-benzoyl-1,2,3,4-tetrahydroisoquinolines,[7] which affords *cis*-8-oxo-13-methylprotoberberines in high yield but does not appear to be adaptable to the preparation of the corresponding trans diastereomers and is also not amenable to the preparation of 9,10-dioxygenated protoberberines without separation from undesired by-products.[7b] In addition, the acid-catalyzed cyclization of a 1-acetyl-2-(2′,3′-dimethoxybenzyl)isoquinolinium bromide has been reported to yield a 9,10-dimethoxy-13-methylbenz[*a*]acridizinium chloride in 20% yield,[8] and a synthesis of oxydehydrocorydaline was described by Koepfli and Perkin in 1928.[9] Thus a method is needed for the preparation of 13-methyltetrahydroprotoberberine alkaloids which would allow control of the stereochemistry at C-13 as well as the substituent pattern in ring D.

As a result of our continuing interest in synthetic applications of the condensation of imines with cyclic carboxylic acid anhydrides[10] and the recently reported antileukemic activity of coralyne and related alkoxydibenzo[*a*,*g*]quinolizinium salts,[11] we now report a convergent synthesis of 13-methyltetrahydroprotoberberines in which the substitution pattern of ring D is dictated by that of a homophthalic anhydride precursor, and also in which the stereochemistry at C-13 is controlled by epimerization of a kinetically produced *trans*-8-oxo-13-carboxytetrahydroprotoberberine intermediate to the thermodynamically more stable cis isomer. Although 3,4-methylenedioxyhomophthalic anhydride[12] and 3,4-dimethoxyhomophthalic anhydride[13] have been prepared, we have initially chosen 4,5-dimethoxyhomophthalic anhydride[14] as starting material because it is presently more accessible.

The condensation of norhydrastinine (**3**) with 4,5-dimethoxyhomophthalic anhydride (**4**) in chloroform at room temperature proceeded exothermally to yield a mixture of *trans*- and *cis*-2,3-methylenedioxy-8-oxo-10,11-dimethoxy-13-carboxytetrahydroprotoberberines (**5** and **6**) from which the major isomer (J_{AB} = 6 Hz) crystallized in 90% yield. Heating this product in refluxing acetic acid resulted in epimerization to the thermodynamically more stable diastereomer (J_{AB} = 4 Hz). By analogy with related protoberberines, the NMR spectrum of the trans isomer is expected to display a larger coupling constant between protons H_A and H_B than the corresponding cis diastereomer,[7a,15,18] and the cis isomer is expected to be thermodynamically more stable.[15]

The kinetic product was therefore tentatively assigned the trans relative configuration **5** while the thermodynamic product was assigned the cis configuration **6**. Since the relative configurations of 13-methyltetrahydroprotoberberines may be unambiguously assigned on the basis of their NMR spectra, the stereochemical assignments may be confirmed by reduction of **5** and **6** to **11** and **12** (Chart I). The trans and cis methyl esters **7** (J_{AB} = 8 Hz) and **8** (J_{AB} = 4 Hz) were obtained by

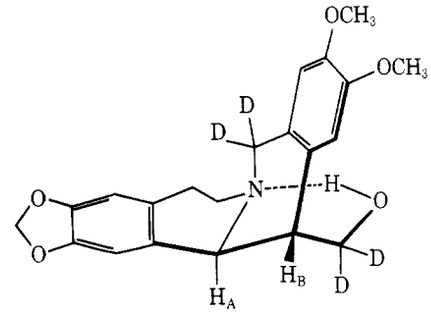
Chart I



a, $CHCl_3$, room temperature (30 min); b, AcOH, reflux (12 h); c, CH_2N_2, Et_2O–EtOH (2 h); d, $LiAlH_4$, Et_2O–THF, reflux (22 h); e, $LiAlH_4$, Et_2O–THF, room temperature (24 h); f, (1) TsCl, Py, room temperature (6.5 h), (2) $LiAlH_4$, THF, reflux (4 h); g, (1) MsCl, Py, room temperature (4 h), (2) $NaCNBH_3$, THF, reflux (16 h).

treatment of the corresponding acids **5** and **6** with diazomethane. Examination of Dreiding models reveals that in contrast to the trans isomer **7**, the pseudoaxial methoxycarbonyl protons of the cis diastereomer can rotate over the aromatic rings A and D. The appearance of the methoxycarbonyl proton signal in the NMR spectrum of **8** at δ 3.40, which is δ 0.40 upfield relative to that of the trans isomer **7**, provides further evidence in support of the relative configuration assignments. Lithium aluminum hydride reduction of esters **7** and **8** provided the corresponding amino alcohols **9** and **10**.

The infrared spectrum of a dilute solution (0.005 M) of **9** in carbon tetrachloride showed a broad hydroxyl stretching absorption near 3300 cm^{-1}, indicating the presence of an intramolecular hydrogen bond. In addition, the deuterated analogue **13** was prepared by reduction of **7** with lithium

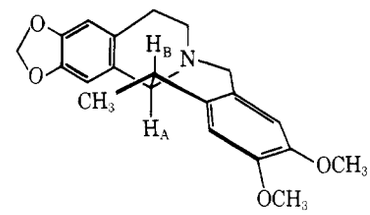


13

aluminum deuteride. The NMR spectrum of **13** in chloroform-*d* displayed a partially resolved doublet (J_{AB} = 2 Hz) at δ 4.30 which was assigned to proton H_A. These observations are only consistent with the conformation represented in structure **13**.

Reduction of the tosylate of **9** with lithium aluminum hydride afforded the *trans*-13-methyltetrahydroprotoberberine **11** in 88% yield, while reduction of the mesylate of **10** with sodium cyanoborohydride gave the cis diastereomer **12**.

The absence of Bohlmann bands[17] in the infrared spectrum of **11**, as well as the appearance of the C-13 methyl group as a doublet (J = 6 Hz) at δ 1.48 and proton H_A as a doublet (J_{AB} = 8 Hz) in the NMR spectrum, establishes the trans relative configuration and cis quinolizidine conformation as shown in structure **14**, whereas the presence of Bohlmann bands at



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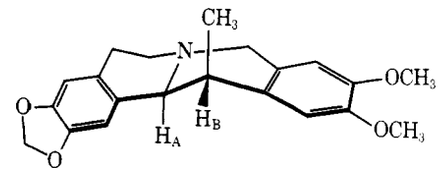

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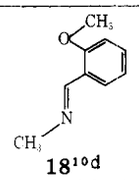
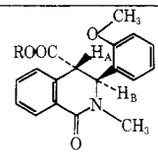
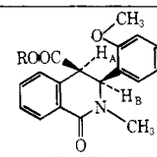
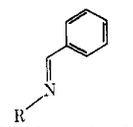
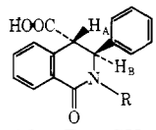
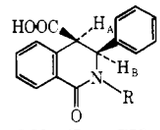
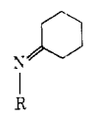
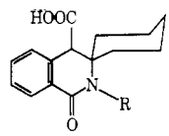
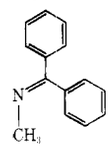
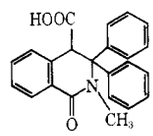
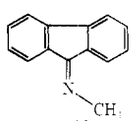
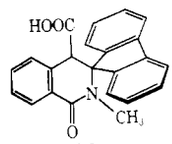
2700–2800 cm^{-1} and the appearance of the C-13 methyl group at δ 0.97 in the NMR spectrum of **12** are only consistent with the cis relative configuration and trans quinolizidine conformation shown in **15**.[16,18]

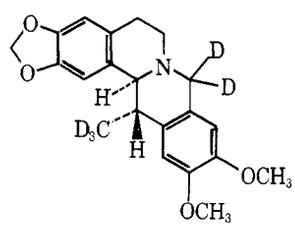
Although it has been observed that in the NMR spectra of cis-9,10-dioxygenated 13-methyltetrahydroprotoberberines the C-8 protons appear as an AB quartet with a large chemical shift difference (0.6–0.7 ppm) and in the corresponding trans diastereomers the difference in chemical shift is much smaller

Table I

Imine	Isoquinolone		% yield[a] (isomer ratio, trans:cis)[b]	Solvent (time, min)	Temp, °C
					
18[10d] (1125-90-2)[c]	**19a**, R = H (60734-28-3) **20a**, R = CH_3 (60734-30-7)	**19b**, R = H (60734-29-4) **20b**, R = CH_3 (60734-31-8)	96 (33:66)	$CHCl_3$ (10)	22
					
21, R = CH_3[23] (622-29-7)	**22a**, R = CH_3 (60734-32-9)	**22b**, R = CH_3 (60734-33-0)	89 (100:0) 89 (50:50)	*p*-Xylene (5) Benzene (15)	137 7
23, R = N=CHC_6H_5[24] (588-68-1)	**24a**, R = N=CHC_6H_5 (60734-34-1)	**24b**, R = N=CHC_6H_5 (60734-35-2)	69 (0:100)	$CHCl_3$ (30)	61
					
25, R = CH_3[25] (6407-35-8) **27**, R = C_6H_5[26] (1132-38-3)	**26**, R = CH_3 (60734-36-3) **28**, R = C_6H_5 (60734-37-4)		85 91	*p*-Xylene (40) *p*-Xylene (30)	137 137
					
29[27] (13280-16-5)	**30** (60734-38-5)		50	*p*-Xylene (30)	137
					
31[28] (60734-27-2)	**32** (60734-39-6)		90	$CHCl_3$ (10)	23

[a] The values reported refer to yields of the crude reaction products, isolated by filtration and drying. [b] The ratio of the diastereomers was determined by integration of the *N*-methyl proton signals in the NMR spectrum. [c] Registry no.

(0.1–0.2 ppm),[18] we have observed exactly the opposite when comparing the 10,11-dioxygenated compounds **11** and **12.** At 60 MHz the C-8 protons of **11** appeared as two doublets (J = 16 Hz) at δ 4.22 and 3.73, with the higher field doublet overlapping the signal for the C-14 proton H_A. These assignments were confirmed by the NMR spectrum of **16,** prepared by



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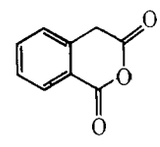
lithium aluminum deuteride reduction of the tosylate of **13.** In contrast, the C-8 protons of **12** were assigned to a broad singlet which appeared at δ 3.72 ppm.

We have also studied the condensation of a variety of aldimines and ketimines with homophthalic anhydride (**17**) as a general synthesis of substituted 4-carboxy-3,4-dihydro-1(2*H*)isoquinolones (Table I). Addition of **17** to a solution of



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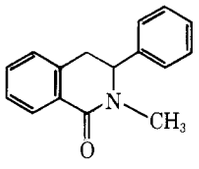
o-methoxybenzylidenemethylamine (**18**) in chloroform at room temperature resulted in a rapid exothermic reaction. The resulting mixture (1:2) of *trans*- and *cis*-*N*-methyl-3-(*o*-methoxyphenyl)-4-carboxy-3,4-dihydro-1(2*H*)isoquinolones (**19a** and **19b**) was isolated by filtration after 10 min in 96% yield and could be separated by fractional crystallization into the minor (J_{AB} = 1 Hz) and major (J_{AB} = 6 Hz) diastereomers. On heating in refluxing acetic acid, the mixture was converted completely into the minor diastereomer. Pure methyl esters **20a** and **20b** were prepared by treatment of the minor and major diastereomers **19a** and **19b** with diazomethane. Heating either compound at 165 °C for 3 h in the absence of solvent yielded a 97:3 mixture of esters of the minor and major diastereomers, respectively, as evidenced by integration of the methoxycarbonyl protons in the NMR spectra of the resulting mixture. We assume that the trans isomers **19a** and **20a** would be the thermodynamically more stable and

assign the minor diastereomer (J_{AB} = 1 Hz) the trans relative configuration. The observed coupling constants for the trans (J_{AB} = 1 Hz) and cis (J_{AB} = 6 Hz) isomers **19a, 19b** and **20a, 20b** are in close agreement with those reported for related pyrrolidinones[10a-c] and piperidones.[10d,e] The small coupling constant observed for the trans isomer **19a** is also in agreement with a preferred conformation in which the carboxyl and aromatic substitutents occupy the pseudoaxial orientations. By analogy to the effect of A strain in cyclohexenes,[19] the vicinal nonbonded interaction between the *N*-methyl substituent and the aromatic ring is expected to force the latter into the pseudoaxial conformation.

Similarly, the reaction of benzylidenemethylamine (**21**) with homophthalic anhydride for 5 min in refluxing *p*-xylene afforded a homogeneous reaction mixture from which only the trans (J_{AB} = 1 Hz) isomer **22a** precipitated on cooling, whereas isolation of the cis isomer **22b** was favored if the reaction mixture was conducted at 7 °C in benzene for 15 min. Finally, reaction of dibenzalhydrazine (**23**) with homophthalic anhydride in refluxing chloroform resulted in isolation of only the cis (J_{AB} = 6 Hz) isomer **24b,** which was quantitatively converted to the trans isomer **24a** (J_{AB} = 2 Hz) when heated in refluxing dimethylformamide for 5 min.

The signal for proton H_A of the cis diastereomers **19b, 22b,** and **24b** appeared near δ 4.8 ppm in the NMR spectra, whereas in the trans isomers **19a, 22a,** and **24a** it was observed upfield at about δ 4.2 ppm. This observation is also in agreement with the above relative configuration assignments, since in the trans diastereomers proton H_A should be shielded by the vicinal aromatic substituent at C-3.[19] In addition, the carboxyl carbon of the cis diastereomer **22b** appeared at δ 170.58 ppm in its ^{13}C NMR spectrum, which is upfield relative to the δ 172.18 ppm observed for the corresponding trans isomer **22a.**[20] Steric compression of the carboxyl carbon of the cis isomer would be expected to shield it relative to the trans isomer.[21]

All of the isoquinolones prepared in the present study decomposed with gas evolution on melting, suggesting decarboxylation. The decarboxylation product **33** was isolated in



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moderate yield after the trans isoquinolone **22a** was heated at 225 °C for 30 min.

We have also investigated the cytotoxicity of protoberberines **5–12** in mammalian cell culture, and the results of these studies will be reported elsewhere.

Experimental Section

All reactions were performed under a nitrogen atmosphere, and solvents were evaporated on a rotary evaporator under vacuum. Melting points were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument, and, except where noted, in $CDCl_3$ solvent. ^{13}C NMR spectra were recorded on a JEOL PFT-100 spectrometer, using Me_2SO-d_6 as solvent. 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. Microanalyses were performed by the Purdue Microanalytical Laboratory. The analytical samples were dried over P_2O_5 at 100 °C (0.1 mm) overnight. The mass spectra were determined on a CEC 21-110 spectrometer using an ion source temperature of 190–260 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA.

***trans*-2,3-Methylenedioxy-8-oxo-10,11-dimethoxy-13-carboxytetrahydroprotoberberine (5).** 4,5-Dimethoxyhomophthalic anhydride (**4**,[14] 22.22 g, 0.1 mol) was added to a stirred solution of norhydrastinine (**3**[22] 17.52 g, 0.1 mol) in $CHCl_3$ (100 ml). An exothermic reaction occurred as the anhydride dissolved. After 30 min the colorless solid (35.87 g, 90%), mp 255–258 °C, was filtered. The analytical sample was recrystallized from AcOH: mp 265–266 °C; IR (KBr) 3300–2500, 3070, 1725, 1615 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5, 5:2) δ 12.15 (s, 1 H, exchangeable with D_2O), 7.72 (s, 1 H), 7.02 (s, 1 H), 6.97 (s, 1 H), 6.60 (s, 1 H), 5.82 (m, 2 H), 5.43 (d, 1 H, J_{AB} = 6 Hz), 4.87 (m, 1 H), 4.28 (d, 1 H, J_{AB} = 6 Hz), 3.83 (s, 6 H), 2.93 (m, 3 H); mass spectrum *m/e* (rel intensity) 397 (M^+, 10), 351 (2), 222 (32), 194 (18), 178 (62), 176 (72), 175 (69), 174 (62), 150 (100).

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.34; H, 4.92; N, 3.48.

***cis*-2,3-Methylenedioxy-8-oxo-10,11-dimethoxy-13-carboxytetrahydroprotoberberine (6).** The trans acid **5** (20 g) was heated in refluxing AcOH (500 ml) for 12 h. The solution was concentrated to 100 ml and the precipitate (18 g, 90%) filtered and washed with EtOH (2 × 100 ml): mp 261–263 °C; IR (KBr) 3600–2500, 2900, 1715, 1610 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5, 5:2) δ 12.26 (s, 1 H, exchangeable with D_2O), 7.85 (s, 1 H), 7.03 (s, 1 H), 6.98 (s, 1 H), 6.62 (s, 1 H), 5.85 (m, 2 H), 5.22 (d, 1 H, J_{AB} = 4 Hz), 4.93 (m, 1 H), 4.30 (d, 1 H, J_{AB} = 4 Hz), 3.82 (s, 6 H), 2.83 (m, 3 H); mass spectrum *m/e* rel intensity) 397 (M^+, 6), 351 (16), 222 (16), 194 (25), 178 (24), 177 (13), 176 (100), 150 (19).

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.41; H, 4.98; N, 3.41.

***trans*-2,3-Methylenedioxy-8-oxo-10,11-dimethoxy-13-methoxycarbonyltetrahydroprotoberberine (7).** The trans acid **5** (10.42 g, 26.25 mmol) was slowly added to a solution of diazomethane (ca. 3 g) in Et_2O–EtOH at 0 °C. EtOH (10 ml) was added and the reaction mixture was stirred occasionally for 2 h at 0 °C. The excess diazomethane was decomposed by addition of AcOH and the reaction mixture concentrated to ca. 15 ml. The colorless solid (10.04 g, 93%) was filtered and washed with Et_2O (2 × 30 ml): mp 205–207 °C; IR (KBr) 2920, 1735, 1645 cm^{-1}; NMR δ 7.67 (s, 1 H), 6.67 (m, 3 H), 5.95 (s, 2 H) 5.23 (d, 1 H, J_{AB} = 8 Hz), 4.87 (m, 1 H), 4.08 (d, 1 H, J_{AB} = 8 Hz), 3.95 (s, 6 H), 3.80 (s, 3 H), 2.93 (m, 3 H); mass spectrum *m/e* (rel intensity) 411 (M^+, 8), 352 (7), 351 (7), 237 (15), 236 (100), 208 (31), 193 (80).

***cis*-2,3-Methylenedioxy-8-oxo-10,11-dimethoxy-13-methoxycarbonyltetrahydroprotoberberine (8).** The cis acid (11.92 g, 30 mmol) was methylated using the same procedure as for preparation of **7,** resulting in a colorless solid (11.32 g, 92%): mp 201–203 °C; IR (KBr) 2940, 1725, 1640 cm^{-1}; NMR δ 7.73 (s, 1 H), 6.85 (s, 1 H), 6.77 (s, 1 H), 6.70 (s, 1 H), 6.00 (s, 2 H), 5.17 (d, 1 H, J_{AB} = 4 Hz), 4.87 (m, 1 H), 4.10 (d, 1 H, J_{AB} = 4 Hz), 3.98 (s, 6 H), 3.40 (s, 3 H), 2.90 (m, 3 H); mass spectrum *m/e* (rel intensity) 411 (M^+, 89), 352 (41), 351 (39), 237 (82), 236 (100), 208 (99), 193 (99).

***trans*-2,3-Methylenedioxy-10,11-dimethoxy-13-hydroxymethyltetrahydroprotoberberine (9).** The trans methyl ester **7** (3.66 g, 8.9 mmol) was added to a solution of $LiAlH_4$ (1.01 g, 26.6 mmol) in Et_2O–THF (1:4, 200 ml). The reactinn mixture was heated at reflux for 22 h before decomposition by dropwise addition of H_2O (1 ml), 15% NaOH (1 ml), and H_2O (3 ml) at 0 °C. The solid was filtered and washed with $CHCl_3$ (3 × 40 ml). The combined filtrates were dried ($MgSO_4$) and the solvent evaporated, leaving a pale green glass. Trituration dded to a solution of $LiAlH_4$ (1.01 g, 26.6 mmol) in Et_2O–THF (1:4, 200 ml). The reaction mixture was heated at reflux for 22 h before decomposition by dropwise addition of H_2O (1 ml), 15% NaOH (1 ml), and H_2O (3 ml) at 0 °C. The solid was filtered and washed with $CHCl_3$ (3 × 40 ml). The combined filtrates were dried ($MgSO_4$) and the solvent evaporated, leaving a pale green glass. Trituration with MeOH afforded a white solid (2.89 g, 88%): mp 183–185 °C; IR 3210, 2900 cm^{-1}; NMR δ 6.82 (s, 1 H), 6.67 (s, 1 H), 6.62 (s, 1 H), 6.50 (s, 1 H), 5.90 (m, 2 H), 4.30 (s, 1 H, exchangeable with D_2O), 4.30 (d, 1 H, J_{AB} = 2 Hz), 4.12 (m, 2 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.70 (s, 2 H), 3.25 (m, 3 H), 2.80 (m, 2 H); mass spectrum *m/e* (rel intensity) 369 (M^+, 29), 338 (18), 195 (100), 194 (7), 179 (17), 177 (15), 176 (23), 174 (13), 165 (38).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.03; H, 6.54; N, 3.50.

***cis*-2,3-Methylenedioxy-10,11-dimethoxy-13-hydroxymethyltetrahydroprotoberberine (10).** The cis ester **8** (11.20 g, 27.2 mmol) was added to a solution of $LiAlH_4$ (2.05 g, 54 mmol) in THF–Et_2O (4:1, 250 ml). The reaction mixture was stirred for 24 h at room temperature. After cooling to 0 °C, H_2O (2 ml), 15% NaOH (2 ml), and H_2O (6 ml) were added dropwise. The solid was filtered and washed with $CHCl_3$ (2 × 50 ml). The combined filtrates were dried ($MgSO_4$) and evaporated. The glassy residue crystallized from EtOH (60 ml) as a light yellow solid (7.73 g, 77%): mp 163–165 °C; IR (KBr) 3150, 2900 cm^{-1}; NMR δ 6.77 (s, 1 H), 6.63 (s, 3 H), 5.93 (s, 2 H), 5.57 (broad s, 1 H, exchangeable with D_2O), 3.90 (m, 9 H), 3.72 (m, 2 H), 3.12 (m, 3

H), 2.62 (m, 2 H); mass spectrum *m/e* (rel intensity), 369 (56), 338 (31), 195 (28), 194 (100), 179 (22), 177 (18), 176 (26), 174 (17), 165 (47).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; H, 6.28; N, 3.79. Found: C, 68.18; H, 6.48; N, 3.90.

***trans*-2,3-Methylenedioxy-10,11-dimethoxy-13-methyltetrahydroprotoberberine (11).** *p*-Toluenesulfonyl chloride (3.43 g, 18 mmol) was added to a solution of the trans alcohol **9** (3.32 g, 9 mmol) in pyridine (90 ml). After 6.5 h at room temperature the reaction mixture was poured into 5% aqueous K_2CO_3 (900 ml). The aqueous layer was extracted with $CHCl_3$ (4 × 200 ml). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated. The last trace of pyridine was removed at 0.1 mm. To the residue was added THF (300 ml) and $LiAlH_4$ (1.37 g, 36 mmol) and the mixture was heated at reflux for 4 h. The reaction mixture was cooled to 0 °C before dropwise addition of H_2O (1.3 ml), 15% NaOH (1.3 ml), and H_2O (3.9 ml). The solid was filtered off and washed with THF (50 ml). The combined filtrates were dried ($MgSO_4$) and evaporated, leaving a light yellow solid residue (2.80 g, 88%), mp 172–175 °C. The analytical sample was recrystallized from C_6H_6: mp 181–182 °C; IR ($CHCl_3$) 2900 cm^{-1}; NMR ($CDCl_3$) δ 6.80 (s, 2 H), 6.67 (s, 1 H), 6.60 (s, 1 H), 5.95 (s, 2 H), 4.22 (d, 1 H, J = 16 Hz), 3.90 (s, 6 H), 3.73 (d, 1 H, J = 16 Hz), 3.67 (d, 1 H, J_{AB} = 8 Hz), 2.97 (m, 4 H), 1.48 (d, 3 H, J = 6 Hz); mass spectrum *m/e* (rel intensity) 353 (M^+, 21), 179 (20), 178 (100), 163 (10), 91 (6).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.79. Found: C, 71.57; H, 6.84; N, 3.95.

***cis*-2,3-Methylenedioxy-10,11-dimethoxy-13-methyltetrahydroprotoberberine (12).** Methanesulfonyl chloride (115 mg, 1 mmol) was added to a solution of the cis alcohol **10** (185 mg, 0.5 mmol) in pyridine (5 ml). The solution was stirred at room temperature for 4 h and then poured into 5% aqueous K_2CO_3 (50 ml). The aqueous layer was extracted with $CHCl_3$ (4 × 10 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The last trace of pyridine was evaporated at 0.1 mm. To the residue was added THF (10 ml) and $NaCNBH_3$ (63 mg, 1 mmol). The mixture was heated at reflux for 16 h, cooled to room temperature, and decomposed by addition of 5 N HCl (5 ml). After stirring at room temperature for 1 h, the mixture was cooled on an ice bath, and NaOH (2 g) added, followed by H_2O (5 ml). The organic layer was separated and the aqueous layer washed with $CHCl_3$ (2 × 10 ml). The combined organic layers were dried ($MgSO_4$) and evaporated, leaving a pale yellow oil (159 mg). This residue was purified by thin layer chromatography [SiO_2, Analtech, 20 × 20 cm, 1000 μ, $CHCl_3$–EtOH (99:1), 2 plates]. The R_f 0.26 band was removed from the plates and the SiO_2 washed with MeOH (50 ml) and filtered. The filtrate was concentrated to 0.5 ml, yielding a colorless solid (83 mg, 47%): mp 155–156 °C; IR ($CDCl_3$) 2880, 2800–2700 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 6.77 (s, 1 H), 6.73 (s, 1 H), 6.65 (s, 2 H), 5.97 (s, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), ca. 3.88 (1 H), 3.72 (s, 2 H), 3.40–2.27 (m, 5 H), 0.97 (d, 3 H, J = 7 Hz); mass spectrum *m/e* (rel intensity) 353 (M^+, 12), 338 (22), 179 (16), 178 (100), 163 (69), 91 (57).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.79. Found: C, 71.09; H, 6.78; N, 3.95.

***trans*-2,3-Methylenedioxy-10,11-dimethoxy-13-hydroxymethyltetrahydroprotoberberine-*8,8,13-hydroxymethyl-d*$_4$ (13).** The trans methyl ester **7** (617 mg, 1.5 mmol) was added to a solution of $LiAlD_4$ (189 mg, 4.5 mmol) in Et_2O–THF (1:1, 30 ml). The reaction mixture was heated at reflux for 23 h and then cooled on an ice bath before dropwise addition of H_2O (1 ml), 15% NaOH (1 ml), and H_2O (3 ml). The solid was filtered and washed with $CHCl_3$ (2 × 10 ml). The combined organic layers were dried (Na_2SO_4) and evaporated, leaving a pale green glass. Trituration with MeOH resulted in crystallization of a light yellow colored solid (432 mg, 77%): mp 184–185 °C; NMR δ 6.82 (s, 1 H), 6.67 (s, 1 H), 6.62 (s, 1 H), 6.50 (s, 1 H), 5.90 (m, 2 H), 4.90 (s, 1 H, exchangeable with D_2O), 4.30 (d, 1 H, J_{AB} = 2 Hz), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.25 (m, 3 H), 2.80 (m, 2 H).

***trans*-2,3-Methylenedioxy-10,11-dimethoxy-13-methyltetrahydroprotoberberine-*8,8,13-methyl-d*$_5$ (16)** *p*-Toluenesulfonyl chloride (381.3 mg, 2 mmol) was added to a solution of **13** (373 mg, 1 mmol) in pyridine (10 ml). After stirring at room temperature for 4 h, the solution was added to 5% aqueous K_2CO_3 (100 ml). The aqueous layer was extracted with $CHCl_3$ (4 × 20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated, with the last trace of pyridine being removed at 0.1 mm. To the residue was added THF (25 ml) and $LiAlD_4$ (168 mg, 4 mmol). The mixture was heated at reflux for 4 h before it was cooled on an ice bath and decomposed by dropwise addition of H_2O (150 μl), 15% NaOH (150 μl), and H_2O (450 μl). The solid was filtered off and washed with THF (10 ml). The combined filtrates were dried ($MgSO_4$) and evaporated, yielding a glass which crystallized on trituration with MeOH as a pale yellow colored solid (165 mg, 46%): mp 182–183 °C; NMR δ 6.80 (s, 2 H), 6.67 (s, 1 H), 6.60 (s, 1 H), 5.95 (s, 2 H), 3.90 (s, 6 H), 3.67 (d, 1 H, J_{AB} = 8 Hz), 2.97 (m, 4 H).

General Procedure for the Synthesis of 2,3-Disubstituted and 2,3,3-Trisubstituted 4-Carboxy-3,4-dihydro-1(2*H*)-isoquinolones. Homophthalic anhydride (1.62 g, 10 mmol) was added to stirred solutions of the imines (10 mmol) in $CHCl_3$, benzene, or *p*-xylene (10 ml) and the reaction mixtures treated as described in Table I. The crude solid reaction products were isolated by filtration of the reaction mixtures at room temperature.

***trans*-*N*-Methyl-3-(*o*-methoxyphenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (19a).** The crude product **19** (10.0 g) containing cis and trans diastereomers (2:1) was heated in refluxing AcOH (125 ml) for 10 h, after which NMR analysis showed the presence of only the trans isomer **19a.** The reaction mixture was filtered hot and the filtrate diluted with H_2O (125 ml). After standing at room temperature overnight, the crystalline solid (7.91 g) was filtered off and washed with H_2O (50 ml): mp 231–232 °C dec; IR 3300–2500, 2970, 1730, 1620, 750 cm^{-1}; NMR ($CDCl_3$–Py-d_5, 1:1) δ 8.57 (s, 1 H, J = 1 Hz exchangeable with D_2O), 8.27 (m, 1 H), 7.08 (m, 7 H), 5.83 (d, 1 H, J = 1 Hz), 4.20 (d, 1 H, J = 1 Hz), 3.83 (s, 3 H), 3.20 (s, 3 H); mass spectrum *m/e* (rel intensity) 311 (M^+, 100), 267 (90), 266 (75) 250 (95), 248 (95).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.19; H, 5.40; N, 4.41.

***trans*-*N*-Methyl-3-(*o*-methoxyphenyl)-4-methoxycarbonyl-3,4-dihydro-1(2*H*)-isoquinolone (20a).** An excess of CH_2N_2 in Et_2O (70 ml) was added to the trans acid **19a** (3.11 g, 10 mmol). After standing at room temperature for 1 h, the reaction mixture was concentrated to 25 ml. The colorless crystals (2.97 g, 91%), mp 144–145 °C, were filtered and washed with Et_2O (2 × 10 ml). The analytical sample was recrystallized once from MeOH: mp 144–145 °C; IR 2925, 1720, 1640, 740 cm^{-1}; NMR δ 8.17 (m, 1 H), 7.10 (m, 7 H), 5.60 (d, 1 H, J = 1 Hz), 4.03 (d, 1 H, J = 1 Hz), 3.92 (s, 3 H), 3.70 (s, 3 H), 3.13 (s, 3 H); mass spectrum *m/e* (rel intensity) 325 (M^+, 9), 266 (60), 176 (35), 148 (100), 133 (74).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 4.89; N, 4.30. Found: C, 70.03, H, 4.69; N, 4.50.

***cis*-*N*-Methyl-3-(*o*-methoxyphenyl)-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (19b).** The crude product **19** (2 g) containing cis and trans diastereomers (2:1) was dissolved in hot EtOH (100 ml). The solution was filtered hot and the filtrate allowed to stand at room temperature for 2 days. The colorless crystals (0.52 g) were filtered: mp 228–229 °C dec; IR 3300–2500, 2960, 1730, 1620, 740 cm^{-1}; NMR ($CDCl_3$–Py-d_5, 1:1) δ 10.48 (s, 1 H, exchangeable with D_2O), 8.47 (m, 1 H), 7.08 (m, 7 H), 5.73, (d, 1 H, J = 6 Hz), 4.78 (d, 1 H, J = 6 Hz), 3.62 (s, 3 H), 3.05 (s, 3 H); mass spectrum *m/e* (rel intensity) 311 (M^+, 5), 151 (86), 135 (100), 119 (38), 106 (86).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.42; H, 5.31; N, 4.60.

***cis*-*N*-Methyl-3-(*o*-methoxyphenyl)-4-methoxycarbonyl-3,4-dihydro-1(2*H*)-isoquinolone (20b).** An excess of CH_2N_2 in Et_2O–EtOH (30 + 2 ml) was added to the acid **20a** (1.0 g, 3.21 mmol). After 6 h, the volume of the reaction mixture was reduced to 5 ml and the solid (0.78 g, 75%) filtered. The analytical sample was recrystallized from MeOH: mp 150–151 °C; IR 2945, 1730, 1635, 735 cm^{-1}; NMR δ 8.25 (m, 1 H), 7.08 (m, 7 H), 5.55 (d, 1 H, J = 6 Hz), 4.68 (d, 1 H, J = 6 Hz), 3.80 (s, 3 H), 3.62 (s, 3 H), 3.02 (s, 3 H); mass spectrum *m/e* (rel intensity) 325 (M^+, 3), 266 (20), 176 (43), 148 (100), 133 (94).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.11; H, 6.09; N, 4.48.

***trans*-*N*-Methyl-3-phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (22a).** The crude product resulting from the condensation of **21** with homophthalic anhydride in refluxing *p*-xylene was recrystallized twice from 2-butanone yielding analytically pure solid: mp 207 °C dec; IR 3300–2500, 2990, 1725, 1645 cm^{-1}; NMR δ 11.12 (s, 1 H, exchangeable with D_2O), 8.12 (m, 1 H), 7.17 (m, 8 H), 5.27 (d, 1 H, J = 1 Hz), 3.95 (d, 1 H, J = 1 Hz), 3.12 (s, 3 H); mass spectrum *m/e* (rel intensity), 281 (M^+, 100), 252 (45), 236 (73), 178 (53), 160 (94).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.63; H, 5.31; N, 5.18.

***cis*-*N*-Methyl-3-phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (22b).** The crude product (11.30 g) resulting from the condensation of **21** with homophthalic anhydride in benzene at 7 °C was recrystallized from EtOH (75 ml), yielding the pure cis diastereomer (0.75 g): mp 201–202 °C dec; IR 3300–2500, 2990, 1725, 1645 cm^{-1}; NMR δ 14.27 (s, 1 H, exchangeable with D_2O), 8.23 (m, 1 H), 7.40 (m, 3 H), 7.15 (s, 5 H), 5.08 (d, 1 H, J_{AB} = 6 Hz), 4.73 (d, 1 H, J_{AB}

= 6 Hz), 3.07 (s, 3 H).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.80; H, 5.30; N, 5.10.

***cis*-*N*-Benzylideneamino-3-phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (24b).** The crude product, mp 203 °C dec, was filtered and washed with a mixture of Et_2O and pentane (1:1, 2 × 20 ml). The analytical sample was recrystallized from AcOH: mp 206 °C dec; IR 3300–2500, 2940, 1720, 1625, 730 cm^{-1}; NMR ($CDCl_3$–Py-d_5, 1:1) δ 11.87 (s, 1 H, exchangeable with D_2O), 9.23 (s, 1 H), 8.50 (m, 1 H), 7.55 (m, 13 H), 6.02 (d, 1 H, J = 6 Hz), 5.02 (d, 1 H, J = 6 Hz); mass spectrum m/e (rel intensity) 370 (M^+, 5), 208 (100), 207 (99), 149 (100), 131 (99).

Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.70; H, 4.95; N, 7.60.

***trans*-*N*-Benzylideneamino-3-phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (24a).** The cis isoquinolone **24b** (1.85 g, 0.05 mol) was dissolved in hot DMF (5 ml) and the solution heated at reflux for 5 min. The solution was cooled to room temperature and the solvent evaporated, leaving a yellow glass. NMR analysis indicated the presence of only the trans isomer. The residue was triturated with benzene (5 ml), resulting in precipitation of a colorless powder (1.51 g), mp 210 °C, which was filtered and washed with benzene (2 × 2 ml). A sample (0.88 g) of the powder was crystallized by dissolving in AcOH (15 ml), filtering, and diluting the filtrate with H_2O (15 ml), yielding colorless crystals (0.64 g): mp 226 °C dec; IR 3300–2500, 2940, 1720, 1625, 730 cm^{-1}; NMR ($CDCl_3$–Py-d_5, 2:1) δ 15.07 (s, 1 H, exchangeable with D_2O), 8.95 (s, 1 H), 8.48 (m, 1 H), 7.38 (m, 13 H), 6.32 (d, 1 H, J_{AB} = 2 Hz), 4.37 (d, 1 H, J_{AB} = 2 Hz).

Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.45; H, 4.99; N, 7.52.

***N*-Methyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone-3-spirocyclohexane (26).** Analytically pure material crystallized after washing the crude product (2.35 g) with benzene (15 ml), dissolving it in hot AcOH (20 ml), filtering, and diluting the filtrate with H_2O (20 ml): mp 202–204 °C dec; IR 3300–2500, 2960, 1700, 1630, 710 cm^{-1}; NMR δ 9.30 (s, 1 H, exchangeable with D_2O), 8.10 (m, 1 H), 7.37 (m, 3 H), 4.23 (s, 1 H), 3.07 (s, 3 H), 1.57 (m, 10 H); mass spectrum m/e (rel intensity) 273 (M^+, 100), 230 (91), 217 (49), 127 (44), 112 (91).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.30; H, 7.23; N, 5.12.

***N*-Phenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone-3-spirocyclohexane (28).** The crude product (3.04 g), mp 237–240 °C dec, was washed with benzene (2 × 15 ml) and dissolved in AcOH (30 ml). Addition of H_2O (30 ml) to the filtered solution resulted in crystallization of analytically pure product (2.71 g): mp 238–240 °C dec; IR 3300–2500, 2960, 1710, 1610, 740 cm^{-1}; NMR δ 10.80 (s, 1 H, exchangeable with D_2O), 8.17 (m, 1 H), 7.37 (m, 8 H), 4.33 (s, 1 H), 1.42 (m, 10 H); mass spectrum m/e (rel intensity) 335 (M^+, 87), 292 (67), 234 (53), 173 (100), 134 (87).

Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.05; H, 6.42; N, 4.18.

***N*-Methyl-3,3-diphenyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone (30).** The analytical sample was recrystallized from 2-butanone: mp 253–255 °C dec; IR 3300–2500, 2980, 1725, 1620, 740 cm^{-1}; NMR δ 9.50 (s, 1 H, exchangeable with D_2O), 8.13 (m, 1 H), 7.33 (m, 13 H), 4.80 (s, 1 H), 3.17 (s, 3 H); mass spectrum m/e (rel intensity) 357 (M^+, 4), 236 (73), 196 (100), 165 (53), 118 (100).

Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.23; H, 5.49; N, 3.80.

***N*-Methyl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolone-3-spiro-9′-fluorene (32).** The crude product (3.80 g), mp 273–276 °C dec, was dissolved in hot AcOH (50 ml). Addition of H_2O (50 ml) to the filtered solution was followed by crystallization of the analytical sample: mp 271–273 °C dec; IR 3300–2500, 2965, 1725, 1610, 730 cm^{-1}; NMR δ 12.40 (s, 1 H, exchangeable with D_2O), 8.50 (m, 1 H), 7.27 (m, 11 H), 4.07 (s, 1 H), 2.70 (s, 3 H).

Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.79; H, 5.00; N, 4.00.

***N*-Methyl-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (33).** The isoquinolone **22a** (2.81 g, 10 mmol) was heated neat at 255 °C for 30 min during which time gas evolved from the melt. The residue was cooled to room temperature and triturated with H_2O (5 ml). The suspension was left standing overnight before filtration of light yellow solid (1.57 g, 66%), mp 105–113 °C. Analytically pure colorless solid was obtained after two recrystallizations from benzene–hexane: mp 118–119 °C; IR 3020, 1650, 730 cm^{-1}; NMR δ 8.15 (m, 1 H), 7.20 (m, 8 H), 4.75 (d of d, 1 H, J = 4,7 Hz), 3.67 (d of d, 1 H, J = 7, 16 Hz), 3.07 (s, 3 H), 2.97 (d of d, 1 H, J = 4, 16 Hz); mass spectrum m/e (rel intensity) 237 (M^+, 80), 160 (60), 118 (100).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.09; H, 6.67; N, 6.00.

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Registry No.—**3,** 6882-28-6; **4,** 5653-42-9; **5,** 60734-40-9; **6,** 60734-41-0; **7,** 60734-42-1; **8,** 60734-43-2; **9,** 60734-44-3; **10,** 60734-45-4; **11,** 60734-46-5; **12,** 60734-47-6; **13,** 60734-48-7; **16,** 60734-49-8; **33,** 21868-89-3; homophthalic anhydride, 703-59-3.

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