Synthesis of 1,2,3,4-Tetrahydroisoquinolines

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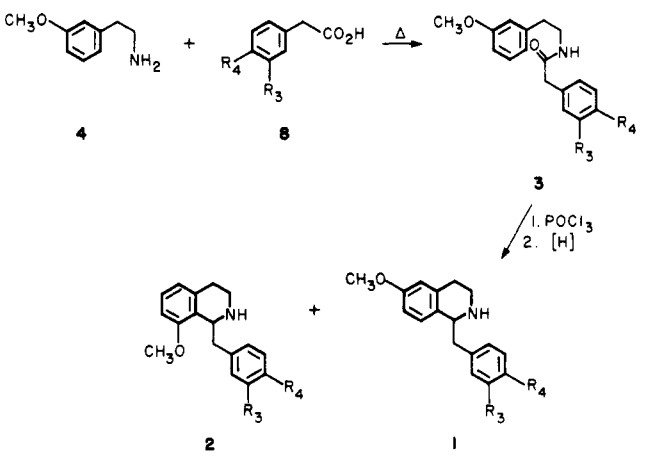
Several aspects of 1,2,3,4-tetrahydroisoquinoline synthesis have been examined. An improved synthesis of 2-(*m*-methoxyphenyl)ethylamine (**4**) is reported. *m*-Anisaldehyde (**5**) was treated with potassium cyanide and ethyl chloroformate to yield *O*-(ethoxycarbonyl)-3-methoxymandelonitrile (**7**). Hydrogenation afforded 2-(*m*-methoxyphenyl)ethylamine (**4**) in 87% yield overall. Some observations have been made regarding the reduction of 3,4-dihydroisoquinolines derived from the Bischler–Napieralski reaction. Amides **3a** and **3c** were cyclized with phosphorus oxychloride, followed by reduction to the corresponding tetrahydroisoquinolines **1a** and **1c**. It was shown that **1a** and **1c** were contaminated with 4% of **2a** and 3% of **2c**, respectively. Both **2a** and **2c** were independently synthesized by routes with general applicability to 8-alkoxy-1,2,3,4-tetrahydroisoquinolines.

Tetrahydroisoquinolines are among the most commonly synthesized natural products, both because of their own biological activity and as precursors to other, more complex alkaloids. Perhaps the most common approach to these compounds has been via the Bischler–Napieralski reaction[1a] (Scheme I). This method proceeds from readily available starting materials and has generally been credited with high yields of pure material. We recently had the need to prepare two alkoxylated tetrahydroisoquinolines, **1a** and **1b**. It soon became obvious to us that certain aspects of the Bischler–Napieralski method were still unsettled and warranted further clarification. The results of our study, as well as the synthetic methodology we developed in obtaining these results, may have potential application to the synthesis of other substituted 1,2,3,4-tetrahydroisoquinolines.

In this report, we describe (1) an improved synthesis of β-phenylethylamines, necessary precursors for the Bischler–Napieralski reaction; (2) some side products frequently formed in the reduction of the intermediate 3,4-dihydroisoquinolines **9**, and the methods devised to prevent their formation; (3) the Bischler–Napieralski reaction of amides **3a** and **3c** (derived from unsymmetrical phenylethylamine (**4**) which yields a mixture of the expected para-cyclized 6-methoxy isomers **1** and 4% of the ortho-cyclized 8-methoxy isomers **2**; and (4) the synthesis of ortho isomers **2a** and **2c** by alternative routes which are particularly applicable to the synthesis of 8-alkoxytetrahydroquinolines.

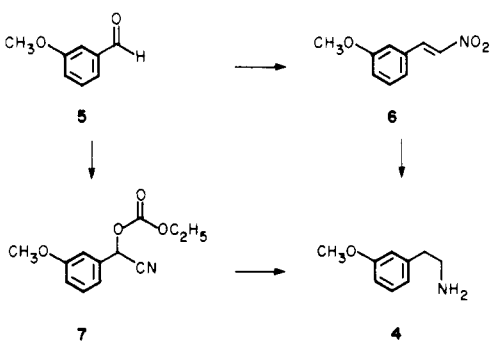
Synthesis of Tetrahydroisoquinolines 1a and 1b. Synthesis of 2-(*m*-Methoxyphenyl)ethylamine (4). Attempted preparation of 2-(*m*-methoxyphenyl)ethylamine (**4**) by reduction of nitrostyrene **6** with lithium aluminum hydride[2] gave a product containing a persistent impurity which could be eliminated only if nitrostyrene **6** was rigorously purified. Catalytic hydrogenation[3] of **6** gave variable results as the scale was increased. However, an efficient and convenient synthesis of phenylethylamine **4**, independent of scale, proceeded in high yield from *m*-anisaldehyde (**5**) by first treatment with potassium cyanide and ethyl chloroformate to form *O*-(ethoxycarbonyl)-3-methoxymandelonitrile (**7**). Hydrogenation[4] of **7** over palladium on charcoal in ethanol at atmospheric pressure gave **4** reproducibly in 92% yield (Scheme II).

Scheme I[a]



[a] a, $R_3 = R_4 = OCH_3$; b, $R_3 = H$, $R_4 = OH$; c, $R_3 = H$, $R_4 = OCH_2C_6H_5$.

Scheme II



Bischler–Napieralski Cyclization. Amide **3c** was prepared in 90% yield by refluxing a mixture of acid **8c** with phenylethylamine **4** in xylene with azeotropic removal of water. Treatment of amide **3c** with phosphorus oxychloride in toluene at reflux for 15 min or at 80 °C for 90 min led to the formation of **9c**. Upon hydrogenation catalyzed by PtO_2, a mixture of the desired **1c** and the cyclohexylmethyl ether **10** was isolated. Attempts to chromatographically separate **1c** and **10** failed. However, further hydrogenolysis of the mixture catalyzed by 10% Pd/C led to a readily separated 2:1 mixture of **1c** and **10**. Reduction of **9c** with $NaBH_4$ gave only the tetrahydroisoquinoline **1c**.

(1) (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74. (b) In reactions related to the Bischler–Napieralski reaction, this question of isomeric purity has been rarely raised.[1c] Reports exist in which the direction of ring closure was assigned on the basis of UV absorption spectra; however, such a criterion would be insensitive to even substantial amounts of the unexpected 8-substituted product. (c) Kametani, T.; Fukumoto, K.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Wakisaka, K. *J. Chem. Soc. C* **1971**, 1805. (d) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Haga, S.; *J. Heterocycl. Chem.* **1974**, *11*, 1063. (e) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592.

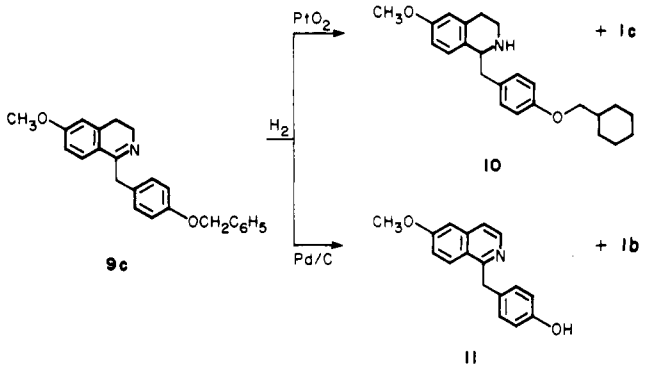
(2) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H. *J. Chem. Soc. C* **1971**, 2632.

(3) Wagner, D. P.; Rachlin, A. I.; Teitel, S. *Synth. Commun.* **1971**, *1*, 47, and references therein.

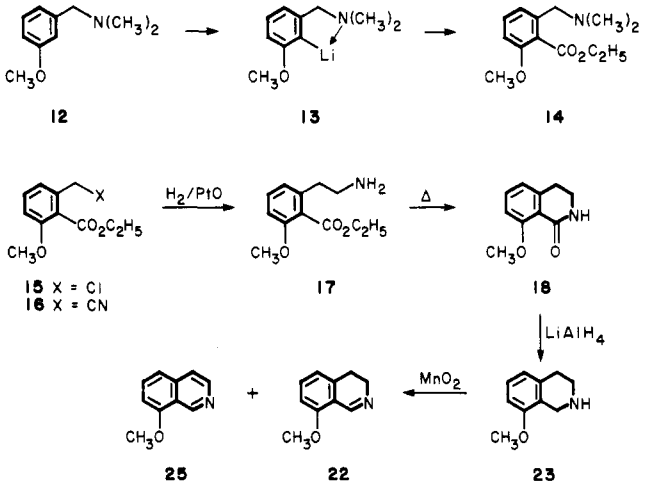
(4) (a) Buck, J. S. *J. Am. Chem. Soc.* **1933**, *55*, 2593. (b) Kindler, K.; Schrader, K. *Justus Liebig's Ann. Chem.* **1949**, *564*, 49.

0022-3263/82/1947-2638$01.25/0

Scheme III



Scheme IV

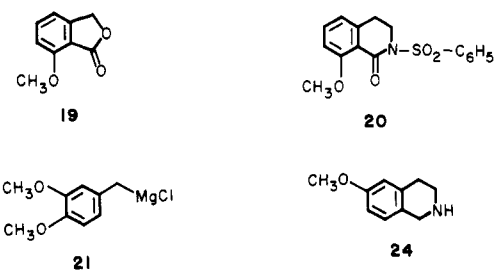


Attempted reduction of the dihydroisoquinoline **9c** directly to **1b** using 10% Pd/C resulted in acceptable yields; however, this reaction was not reliable, and the product frequently was contaminated by an impurity. The UV spectrum of the reaction product showed a strong absorption at 322 nm, indicating the presence of the fully aromatic 6-methoxyisoquinoline (**11**),[5] with some reactions yielding products containing as much as 50% of the undesired **11**. Washing the crude dihydroisoquinoline **9c** repeatedly with alkali to remove residual $POCl_3$ and other phosphorus compounds prior to hydrogenation eliminated the formation of **11**. Under these conditions, **1b** was isolated in 75% yield, free of **11** (Scheme III).

Similarly, heating of amine **4** with acid **8a** in refluxing xylene afforded an 87% yield of amide **3a**. Treatment of **3a** with $POCl_3$ in refluxing toluene yielded the dihydroisoquinoline **9a**. A basic wash of crude **9a**, followed by hydrogenation (PtO_2/H_2/50 psi), afforded a 97% yield of crystalline tetrahydroisoquinoline **1a**.

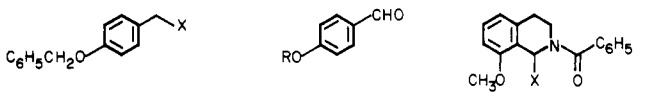
Synthesis of Tetrahydroisoquinolines 2a and 2c. Lithiation[6] (*n*-butyllithium, 0 °C) of benzylamine **12** in THF, followed by quenching with an equivalent of ethyl chloroformate, afforded the benzoate ester **14**. Then treatment of distilled **14** with excess ethyl chloroformate generated benzyl chloride[7] **15**, which with potassium cyanide in DMF gave nitrile **16**. Hydrogenation of **16** to phenylethylamine **17**, which was cyclized in refluxing benzene, yielded 8-methoxy-3,4-dihydroisocarbosytril (**18**) (Scheme IV).

We assumed that if **18** were converted to the sulfonamide **20** it might then be susceptible to attack by the benzylmagnesium chloride **21**. The amide carbonyl of **20** displays an IR absorption at 1690 cm^{-1}, more characteristic of the carbonyl of a ketone than that of amide (**18** has a carbonyl absorption at 1670 cm^{-1}). When **20** was treated with 110 mol % of **21**, however, no reaction occurred.



We then decided to convert amide **18** into amine **22**, confident that the dihydroisoquinoline **22** would react with the benzyl Grignard reagent **21** to yield **2a**. Isocarbostyril **18** was reduced to 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**23**)[9] with lithium aluminum hydride in 93% yield. Oxidation of tetrahydroisoquinoline **23** with MnO_2[11a] in benzene led predominately to the undesired fully aromatized 8-methoxyisoquinoline (**25**). With dichloromethane as solvent, oxidation was more selective, and the desired dihydroisoquinoline **22** was the major product; γ-MnO_2[11b] reacted similarly in CH_2Cl_2. Treatment of this reaction product with the benzyl Grignard reagent **21** afforded a 44% yield of **2a**.

To synthesize **2c**, we planned to add the Grignard reagent **26a** or **26b** to the dihydroisoquinoline **22**. *p*-Hydroxybenzaldehyde (**27**) was treated with benzyl chloride, generating **27b**. Reduction with sodium borohydride afforded alcohol **26c**, which was converted to benzyl chloride **26d** with phosphorus trichloride. Alternatively, stirring alcohol **26c** in ether/48% HBr yielded benzyl bromide **26e**. All attempts at generating the Grignard reagents **26a** and **26b** from **26d** and **26e**, respectively, with activated magnesium[12] or magnesium turnings was un-



26a X = MgCl
26b X = MgBr
26c X = OH
26d X = Cl
26e X = Br
26f X = *p*-$CH_2C_6H_4OBn$

27a R = H
27b R = $CH_2C_6H_5$

28 X = CN
29 X = OH

(5) Nakanishi, K.; Ohashi, M.; Kumasaki, S.; Koike, H. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 533.

(6) (a) Klein, K. P.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 1479. (b) Narashimhan, N. S.; Bhide, B. H. *Tetrahedron Lett.* **1968**, 4159. (c) Ranade, A. C.; Mali, R. S.; Bhide, S. R.; Mehta, S. R. *Synthesis* **1976**, 123.

(7) Treatment of **13** with 200 mol % of ethyl chloroformate provided a 60% yield of benzyl chloride **15** contaminated with 10% of lactone **19**;[8] 200 mol % of methyl chloroformate gave a 73% yield of lactone **19**. Monitoring the reaction by TLC showed that lactone formation was concomitant with chloro ester formation. Lactonization of chloro ester **15** may be facilitated by lithium chloride present in the reaction mixture or may be solely a thermal process (attempted GC purification of **15** at 180 °C yielded lactone **19**). Similar results have been reported by Hinton, I. G. H.; Mann, F. G. *J. Chem. Soc.* **1959**, 599.

(8) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195.

(9) If lithiation of **12** had not been as regioselective as inferred,[6] **23** might be contaminated with 6-methoxy-1,2,3,4-tetrahydroisoquinoline (**24**). A sample of **24** was prepared[10] via the Pictet–Spengler reaction from phenylethylamine **4** and formalin. The compounds were distinguishable by GC, and **23** was shown to be free of **24** (limits of detection, 0.5%). It is possible that both the metalation of **18** and the Pictet–Spengler reaction with **4** were not 100% regiospecific; however, any minor products, if present, were lost during the purifications.

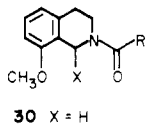
(10) Helfer, L. *Helv. Chim. Acta* **1924**, *7*, 945.

(11) (a) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094. (b) Fatiadi, A. J. *Synthesis* **1975**, 65.

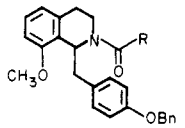
(12) (a) Rieke, R. D. *Fortsch. Chem. Forschung.* **1975**, *59*, 1. (b) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1755.

successful, yielding only bibenzyl **26f**.

Faced with these failures, we explored reversal of the role of each moiety, i.e., using the isoquinoline moiety in a nucleophilic sense and the benzyl halides **26d** or **26e** as the electrophilic species. Attempted synthesis of the Reissert-like[13] compound **28** gave only **29**. Treatment of tetrahydroisoquinoline **23** with benzoyl chloride gave benzamide **30a**, which with LDA resulted in 10% lithiation only at C-1. The yield and regiospecificity[14] of the metalation were determined by a deuterium quench (D_2O) and by trapping with CO_2 to form carboxylic acid **32**.



30 X = H
31 X = Li
32 X = CO_2H



33

a R = C_6H_5
b R = p-$C_6H_4C(CH_3)_3$
c R = $C(CH_3)_3$
d R = p-$C_6H_4C_6H_5$

Since the low yield of metalation was due, at least in part, to the insolubility of benzamide **30a** in THF and other ethereal solvents, 4-*tert*-butylbenzamide **30b** and pivalamide **30c** were prepared. Both exhibited satisfactory solubility in THF, and metalation of these compounds was examined under a variety of conditions. LDA afforded 20% of 1-lithio derivatives **31b** and **31c**, the remainder being unreacted **30b** and **30c**. Use of *n*-butyllithium (−90 °C) resulted primarily in attack at the carbonyl. The best results were obtained with 300 mol % of LDA at −70 °C, giving 40% yields of **31b** and **31c**. Proceeding with the synthesis of **2c**, metalation of **30b** under these conditions, followed by addition of 100 mol % of benzyl bromide **26e**, gave **33b** in 31% yield. Hydrolysis of the 4-*tert*-butylbenzoyl group to generate **2c** proved to be surprisingly difficult. Attempted reductive cleavage[15] with 3% sodium amalgam also failed, giving no reaction.

Assuming that the sodium amalgam reduction was sensitive to the oxidation potential of the amide carbonyl, we returned to tetrahydroisoquinoline **23** and prepared the *p*-phenylbenzamide **30d**. Treatment with 100 mol % of *tert*-butyllithium, followed by addition of **26d**, afforded a 61% yield of **33d** and a 20% yield of recovered starting material. The alkylated product **33d** was reductively cleaved with 3% sodium amalgam to generate the desired **2c**.

Isomer Analysis of Bischler–Napieralski Reaction Product. Compound **2a** was separable from **1a** by HPLC. Careful analysis of the total product (97% mass balance) of the Bischler–Napieralski reaction ($POCl_3$, refluxing toluene, followed by PtO_2-catalyzed hydrogenation) established that 4% of the tetrahydroisoquinoline present was the 8-methoxy isomer **2a**. Similarly, **2c** was separable from **1c** by HPLC, and analysis of the total product (92% mass balance) of the reaction ($POCl_3$, toluene, 80–85 °C, followed by $NaBH_4$ reduction) showed that 3% of the tetrahydroisoquinolines present was the 8-methoxy isomer **2c**. These chromatographic results, together with a comparison of the methoxy absorptions in the NMR for both the 6- and 8-isomers, are summarized in Table I.

Table I. Comparison of Para Cyclization Isomers 1a and 1c with Ortho Isomers 2a and 2c by Chromatography and NMR Absorption of Methyl Ethers

compd	HPLC t_R, min	NMR of aryl methyl ethers
1a·HCl	3.87[a]	3.86 (6 H), 3.91 (3 H)[c]
2a·HCl	2.49[a]	3.68, 3.80, 3.83[c]
1c	3.9[b]	3.73[d]
2c	3.1[b]	3.82[d]

[a] Spectra-Physics Model 3500 B chromatograph; flow rate 1.32 mL/min, chloroform; 250 × 3.2 mm column, Lichrosorb Si-60, 5 μm; limit of detection 0.47%; UV detector at 270 nm; retention times were determined by coinjection of 1a and 2a with base-line separation. [b] Altex Model 332 micropressor controlled HPLC with Hitachi Model 100-10 variable UV detector at 270 nm; Lichrosorb Si-60 column, 5 μm, 250 × 3.2 mm, eluted with 10% hexane in $CHCl_3$ at 1.5 mL/min; retention times were determined by coinjection of 1c and 2c with base-line separation. [c] ^1H NMR in $CDCl_3/Me_4Si$ at 60 MHz. [d] ^1H NMR in $CDCl_3/Me_4Si$ at 90 MHz.

With both compounds **1a** and **1c**, crystallization afforded material free of the 8-methoxytetrahydroisoquinolines **2a** and **2c** in 85 and 82% yield, respectively. Hydrogenolysis of **1c** then afforded a 97% yield of **1b**, thus completing the synthesis of the desired tetrahydroisoquinoline. These results demonstrate that Bischler–Napieralski reaction products derived from unsymmetrically substituted phenylethylamines may contain the ortho-cyclized isomer. This possibility should be considered in their further application.

Experimental Section

All reactions were performed under a nitrogen atmosphere with magnetic stirring unless noted otherwise. Reaction solvents were freshly distilled as follows: $CHCl_3$, CH_2Cl_2, and hexane from P_2O_5; THF from potassium–benzophenone ketyl; benzene from itself. Organic extracts were finally washed with saturated NaCl, dried over $MgSO_4$, and evaporated in vacuo. Melting points are corrected. ^1H NMR spectra were determined with internal Me_4Si in $CDCl_3$ unless otherwise noted. Gas chromatographies were carried out with 80–100 mesh Chromosorb W as support on 5-ft columns with 3% OV-1 (A, glass column), 5% OV-25 (B, glass column), or 5% SE-30 (C, glass column) as the liquid phase. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

***O*-(Ethoxycarbonyl)-3-methoxymandelonitrile (7).** To a stirred solution of 13.6 g (0.1 mol) of *m*-anisaldehyde (**5**) and 11.9 g (0.11 mol, 10.8 mL) of ethyl chloroformate in 20 mL of THF, cooled in an ice–water bath, was added in one portion 7.2 g (0.11 mol) of KCN dissolved in 25 mL of water. The reaction mixture was stirred for 4 h at 5 °C and then slowly warmed to room temperature overnight. Water (100 mL) was added, the aqueous solution was extracted with 3 × 40 mL of ether, the combined extracts were dried and evaporated, and the residue was Kugelrohr distilled to afford 21.4 g (0.92 mol, 92%) of nitrile **7**: bp 110–115 °C (0.3 mm) [lit.[4] bp 132 °C (0.4 mm)]; GC (column A, 170 °C) t_R = 2.1 min; NMR δ 1.28 (3 H, t, J = 6 Hz), 3.75 (3 H, s), 4.22 (2 H, q, J = 6 Hz), 6.17 (1 H, s), 7.07 (4 H, m).

2-(*m*-Methoxyphenyl)ethylamine (4). A solution of 23.5 g (0.1 mol) of **7** in 300 mL of absolute ethanol was added dropwise (0.5 drop/s) to a mechanically stirred solution of 300 mL of absolute ethanol containing 1.5 g of 10% Pd/C catalyst and 12.9 g (0.13 mol, 7 mL) of concentrated sulfuric acid as hydrogen was bubbled through the solution. After the addition, stirring and bubbling were continued for 8 h, the reaction mixture was filtered, the filtrate was evaporated, water (100 mL) was added, and the cooled aqueous solution was made alkaline with 4 M sodium hydroxide. The solution was extracted with 4 × 50 mL of ether, the combined extracts were dried and evaporated, and the residue was Kugelrohr distilled to afford 13.9 g (0.09 mol, 92%) of phenylethylamine **4**: bp 93–95 °C (0.1 mm) [lit.[2] bp 122–123 °C (1.0 mm)]; GC (column B, 140 °C) t_R = 5.4 min; NMR δ 1.25 (2 H,

(13) (a) McEwen, W. E.; Cobb, R. L. *Chem. Rev.* **1955**, *55*, 511. (b) Popp, F. D.; *Adv. Heterocycl. Chem.* **1968**, *9*, 1.
(14) (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Fraser, R. R.; Boussard, G.; Postescu, I. D.; Whiting, J. J.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 1109. (c) Lohmann, J. J.; Seebach, D.; Syfrig, M. A.; Yoshifujii, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 128. (d) Seebach, D.; Yoshifuji, M. *Helv. Chim. Acta* **1981**, *64*, 643. (e) Meyers, A. I.; Hellring, S.; Ten Hoeve, W. *Tetrahedron Lett.* **1981**, *22*, 5115.
(15) Scribner, R. M. *Tetrahedron Lett.* **1976**, 3853.

s), 2.81 (4 H, m), 3.74 (3 H, s), 6.91 (4 H, m).

***N*-[(3-Methoxyphenyl)ethyl]-4-(benzyloxy)phenylacetamide (3c).** A solution of 22.8 g (94 mmol) of *p*-(benzyloxy)-phenylacetic acid (**8c**)[16] and 14.2 g (94 mmol) of 2-(*m*-methoxyphenyl)ethylamine (**4**) in 500 mL of xylene was refluxed for 24 h with H_2O removal. Cooling caused the product to crystallize: yield 35.3 g (90%); mp 93–95 °C; NMR δ 2.66 (2 H, t, J = 7 Hz), 3.40 (4 H, m), 3.70 (3 H, s), 5.00 (2 H, s), 5.39 (1 H, br s), 7.33 (5 H, s), 6.40–7.50 (4 H, m); IR (Nujol) 1630 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.8; H, 6.7; N, 3.7. Found: C, 76.7; H, 6.7; N, 3.7.

1-[4-(Benzyloxy)benzyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1c). To a solution of 1.0 g (2.7 mmol) of amide **3c** in 50 mL of toluene warmed to 80 °C was added 1 mL of $POCl_3$ over a 1-min period. After 2.5 h at 80–85 °C, the reaction mixture was evaporated to an oil, which was dissolved in CH_2Cl_2, and washed (3 × 20 mL of 1 N NaOH, 20 mL of H_2O, 15 mL of saturated NaCl), dried, and evaporated, immediately dissolving the residue in 30 mL of methanol. Over a 30-min period, 0.95 g of $NaBH_4$ was added, and the reaction mixture was allowed to stir for 4 h. After the addition of 30 mL of water, the methanol was evaporated, affording crude **1c**: yield 0.93 g (93%). Crystallization from 1:1 ethanol/10% HCl yielded 0.86 g (82%) of 1c·HCl: mp 194–196 °C; NMR (Me_2SO/Me_4Si) δ 2.90–3.5 (6 H, m), 3.72 (3 H, s), 4.57 (1 H, m), 5.07 (2 H, s), 6.67–7.70 (12 H, m), 9.70 (2 H, br s). Anal. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.8; H, 6.6; N, 3.5. Found: C, 72.9; H, 6.8; N, 3.4.

1-(4-Hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1b). To **1c**·HCl (1 g, 2.5 mmol) dissolved in 50 mL of 2:1 ethanol/water was added 0.5 mL of concentrated HCl and 100 mg of 10% Pd/C. After shaking under 50 psi of H_2 for 18 h, the reaction mixture was filtered, the catalyst was washed well with ethanol, and the filtrate and washings were evaporated to a solid, which was dissolved in 0.5 M NaOH with warming to 40 °C. After filtration, the pH of the filtrate was adjusted to 8 with saturated NH_4Cl, and the resulting precipitate was recrystallized from acetone to give amine **1b**, mp 120–122 °C, or from 1% HCl to give **1b**·HCl, mp 256–257 °C: yield 0.75 g (2.5 mmol, 97%); NMR (Me_2SO-d_6) δ 2.3–3.3, 3.70 (3 H, s), 3.93 (1 H, br s), 6.4–7.3 (7 H, m). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.8; H, 6.6; N, 4.6. Found: C, 66.6; H, 6.6; N, 4.5.

3,4-Dihydro-6-methoxy-1-[4-(benzyloxy)benzyl]isoquinoline (9c). To 600 mL of toluene and 20 g (53 mmol) of *N*-(3-methoxyphenyl)-4-(benzyloxy)phenylacetamide (**3c**), heated to 87 °C, was added, all at once, 20 mL of $POCl_3$. After 1.5 h, the yellow solution was evaporated to a glass. This was used for the reductions described below as is or was crystallized by dissolving the glass in 100 mL of absolute ethanol and 50 mL of concentrated HCl. After the solution was cooled, 15.7 g (0.04 mol, 75%) of **9c**·HCl was obtained: mp 194–196 °C; NMR δ 3.00 (2 H, m), 3.76 (2 H, s), 3.81 (3 H, s), 4.47 (2 H, br s), 4.88 (2 H, s), 6.50–7.50 (12 H, m), 7.83 (*1* H, br s).

1-[4-[(Cyclohexylmethyl)oxy]benzyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (10). To 7.7 g (20.5 mmol) of amide **3c** dissolved in 120 mL of refluxing toluene was added 7.7 mL of $POCl_3$. After 15 min, the solvent was evaporated, 200 mL of 95% ethanol, 110 mL of water, and 350 mg of PtO_2 were added, and the solution was shaken under 50 psi of H_2 for 11 h. The solution was filtered and evaporated until turbidity occurred, and then 10 mL of concentrated HCl was added. Upon warming, the solution became homogeneous, and upon cooling, 5.2 of (65% yield) of **1c**·HCl was isolated as a gummy solid, contaminated with **10**.

To 9 g (22.8 mmol) of this impure **1c**·HCl dissolved in 550 mL of 95% ethanol was added 1 g of 10% Pd/C. The solution was shaken under 50 psi of H_2 for 18 h and then filtered, the filtrate was evaporated, and the resulting solid was then stirred with 200 mL of 10% NaOH and filtered. The residue was digested in boiling acetone and filtered hot. Cooling the acetone gave 2.21 g (26%) of **10**: mp 125–127 °C; ^1H NMR δ 0.9–2.3 (11 H, broad envelope), 2.3–3.5 (6 H, m), 3.75 (3 H, S), 3.70–4.1 (3 H, m), 6.50–7.35 (8 H, m); ^{13}C NMR (acetic acid-d_4) δ 160.1, 160.07, 134.5, 131.9, 129.1, 127.9, 125.0, 116.1, 114.7, 114.4, 74.5, 57.6, 55.9, 40.7, 40.2, 38.9, 30.9, 27.5, 26.8, 26.5. Anal. Calcd. for $C_{24}H_{31}NO_2$: C, 78.9; H, 8.6; N, 3.8. Found: C, 78.8; H, 8.6; N, 3.8. The 10% NaOH solution was neutralized to pH 7.2 with 10% HCl to afford 3.06 g (51%) of **1b**.

Hydrogenation of 9c without Prior Alkali Treatment. Formation of 1b and 11. To a solution of 0.505 g (1.35 mmol) of **3c** in 15 mL of toluene was added 0.5 mL of $POCl_3$. After a 15-min reflux, the solvent was evaporated to an oil, which was then dissolved in 20 mL of ethanol, 2 mL of concentrated HCl and 0.5 g of 10% Pd/C were added, and the mixture was shaken under 50 psi of H_2 for 12 h. Filtration and evaporation left a gummy solid, **1b** contaminated with 11: UV (CH_3OH) λ_{max} 322 nm (ϵ 2990) [lit.[5] for 6-methoxyisoquinoline: UV (CH_3OH) λ_{max} 315 nm (ϵ 5600)]. In seven similar experiments, the amount of **11** in the crude product ranged from 10 to 50%.

6-Methoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (1a). A mixture of 29.0 g (88 mmol) of *N*-(3-methoxyphenethyl)-3,4-dimethoxyphenylacetamide (**3a**)[17] and 32 mL (53.7 g, 0.34 mol) of $POCl_3$ in 200 mL of toluene was heated at reflux for 1.5 h. The reaction mixture was cooled and evaporated, and the brown residue was dissolved in hot 1:1 H_2O/ethanol and hydrogenated over 300 mg of PtO_2 for 12 h at 45 psi of H_2. The hydrogenation mixture was filtered through super cel, the ethanol was evaporated, and the aqueous residue was made alkaline with concentrated NaOH and extracted with 3 × 100 mL portions of ether. The combined ether extracts were washed, dried, and evaporated to give a yellow oil, which was dissolved in 200 mL of THF, and anhydrous HCl was passed in for 1 h. The precipitated hydrochloride was filtered, washed with ether, and air-dried, affording 30.1 g (86 mmol, 97%) of the tetrahydrobenzylisoquinoline hydrochloride, **1a**·HCl, as a light yellow powder: mp 199–200 °C after recrystallization from 1-propanol (lit.[18] mp 177–180 °C); NMR δ 3.21 (6 H, m), 3.86 (6 H, s), 3.91 (3 H, s), 4.95 (1 H, m), 6.82 (6 H, m). Anal. Calcd for $C_{19}H_{23}NO_3Cl$: C, 65.4; H, 6.7; N, 4.0. Found: C, 65.2; H, 6.9; N, 3.9.

To the **1a**·HCl (10 g, 29 mmol) in 100 mL of water was added 10 g (72 mmol) of K_2CO_3, and the cloudy reaction mixture was stirred for 3 h at 25 °C and then extracted with 3 × 50 mL of ether. The combined ether extracts were dried and evaporated, and the residue was crystallized from benzene/hexane to afford 7.7 g (24 mmol, 85%) of pure **1a**: mp 92–93 °C (lit.[17] mp 92–93 °C); NMR δ 3.23 (6 H, m), 3.85 (6 H, s), 3.91 (3 H, s), 4.95 (1 H, s), 6.82 (6 H, m).

***N*,*N*-Dimethyl-2-(Ethoxycarbonyl)-3-methoxybenzylamine (14).** To a solution of 14.2 g (0.086 mol) *N*,*N*-dimethyl-3-methoxybenzylamine (**12**)[6a] in 170 mL of THF cooled in an ice–water bath was added dropwise *n*-butyllithium in hexane (50 mL, 0.087 mol, 1.75 M) over 0.5 h. After an additional hour, the mixture was cooled to −78 °C, and 9.4 g (0.086 mol, 8.3 mL) of ethyl chloroformate was added dropwise over a 15-min period. The reaction mixture was then allowed to warm to room temperature, the solvent was evaporated, and 125 mL of H_2O was added to the residue, followed by extraction with 3 × 25 mL of CH_2Cl_2. The combined organic extracts were washed, dried, and evaporated, and the residue was Kugelrohr distilled, affording 15.7 g (0.66 mol, 77%) of ester **14**: bp 81–85 °C (0.4 mm); NMR δ 2.16 (6 H, s), 2.32 (2 H, s), 3.75 (3 H, s), 4.35 (2 H, q, J = 7 Hz), 6.87 (2 H, m), 7.13 (1 H, m).

2-(Ethoxycarbonyl)-3-methoxybenzyl Chloride (15). To a solution of 15 g (63 mmol) of *N*,*N*-dimethyl-2-(ethoxycarbonyl)-3-methoxybenzylamine (**14**) in 34 mL of chloroform cooled in an ice–water bath was added 7.6 g (70 mmol, 7 mL) of ethyl chloroformate over 15 min, followed by an additional 15 min of stirring. Water (20 mL) was added, and the organic phase was dried and evaporated. Distillation (bulb to bulb) of the residue provided 13.6 g (60 mmol, 94%) of the benzyl chloride **15**: bp 95–100 °C (0.7 mm); NMR δ 1.37 (3 H, t, J = 6 Hz), 3.73 (3 H, s), 4.63 (2 H, q, J = 6 Hz), 4.53 (2 H, s), 6.85 (2 H, m), 7.16 (1 H, m).

2-(Ethoxycarbonyl)-3-methoxyphenylacetonitrile (16). To 2-(ethoxycarbonyl)-3-methoxybenzyl chloride (**15**; 11.8 g, 51.6

(16) Collins, D. J.; Hobbs, J. J. *Aust. J. Chem.* **1967**, *20*, 1413.

(17) Shavel, J.; Morrison, G. C. U.S. Patent 3 438 989; *Chem. Abstr.* **1969**, *71*, 22 236.

(18) Tedeschi, D. H. U.S. Patent 3 272 707; *Chem. Abstr.* **1966**, *65*, 20 109.

mmol) in 52 mL of DMF was added in one portion 20.2 g (0.413 mol) of freshly pulverized NaCN. The reaction mixture was diluted with 250 mL of water after 4 h and extracted with 4 × 80 mL of benzene. The combined organic extracts were washed, dried, and evaporated, and the residue was bulb to bulb distilled, providing 9.9 g (45.2 mmol, 88%) of nitrile **16**: bp 110–112 °C (0.5 mm); NMR δ 1.35 (3 H, t, J = 7 Hz), 3.73 (2 H, s), 3.80 (3 H, s), 4.39 (2 H, q, J = 7 Hz), 6.96 (2 H, m), 7.30 (1 H, m).

3,4-Dihydro-8-methoxyisocarbostyril (18). A solution of 9.9 g (45.2 mmol) of 2-(ethoxycarbonyl)-3-methoxyphenylacetonitrile (**16**) in 100 mL of ethanol containing 4.6 g (46.9 mmol, 2.5 mL) of concentrated sulfuric acid was hydrogenated over 200 mg of PtO_2 at an initial 50 psi of H_2 for 12 h. The reaction mixture was filtered after 8 h, and the filtrate was evaporated. To the cooled residue was added 4 M sodium hydroxide to pH 10, and the alkaline solution was extracted with 3 × 20 mL of CH_2Cl_2. The combined extracts were dried and evaporated, and 50 mL of benzene was added to the residue and refluxed for 3 h. Evaporation and crystallization of the residue from benzene gave 5.95 g (33.6 mmol, 74%) of isocarbostyril **18**: mp 148–149 °C; IR (CH_2Cl_2) 1670 cm^{-1}; NMR δ 2.85 (2 H, m), 3.30 (2 H, m), 3.81 (3 H, s), 6.95 (2 H, m), 7.31 (1 H, m). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.6; H, 6.2; N, 7.9.

***N*-(Benzenesulfonyl)-3,4-dihydro-3-methoxyisocarbostyril (20).** To a suspension of 269 mg (5.6 mmol) of sodium hydride (50% dispersion in mineral oil from which the oil was removed by washing with 2 × 3 mL of hexane) in 10 mL of DMF under a nitrogen atmosphere was added 885 mg (5.0 mmol) of isocarbostyril **18**. The reaction mixture was stirred for 0.5 h at 50 °C and then cooled to 24 °C, and 989 mg (5.6 mmol, 0.72 mL) of benzenesulfonyl chloride was added dropwise, followed by stirring for 1.5 h and then pouring into 15 mL of saturated sodium bicarbonate. After the mixture was stirred for 2 h, the precipitate was removed, washed with 10 mL of water, and air-dried, affording 620 mg of sulfonamide **20**. Extraction of the filtrate with 3 × 10 mL of $CHCl_3$, followed by drying, evaporating, and adding 5 mL of hot absolute ethanol to the residue, afforded an additional 210 mg of sulfonamide upon cooling: total yield 830 mg (2.6 mmol, 52%) of **20**; mp 144–145 °C (from absolute EtOH); IR (CH_2Cl_2) 1690 cm^{-1}; NMR δ 2.95 (2 H, t, J = 7 Hz), 3.80 (3 H, s), 4.15 (2 H, t, J = 7 Hz), 6.73 (2 H, m), 7.38 (4 H, m), 8.01 (2 H, m). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4. Found: C, 60.6; H, 4.9; N, 4.4.

8-Methoxy-1,2,3,4-tetrahydroisoquinoline (23). Lithium aluminum hydride (2.28 g, 60.0 mmol) in 100 mL of THF was treated with 3.54 g (20.0 mmol) of isocarbostyril **18** added in small portions over a 0.5-h period. The reaction mixture was then gently refluxed, after 5 h was cooled in an ice–water bath, and decomposed by the successive dropwise addition of 2 mL of water, 2 mL of 4 M sodium hydroxide, and 6 mL of water. The granular precipitate was removed and washed with 100 mL of THF, the filtrate was evaporated, and the residue was Kugelrohr distilled, yielding 3.1 g (18.7 mmol, 93%) of tetrahydroquinoline **23**: bp 73–76 °C (65 μm), which solidified upon standing at −5 °C: mp 38–39 °C; GC (column C, 150 °C) t_R = 2.4 min; NMR δ 1.58 (1 H, s), 2.75 (2 H, d, J = 5 Hz), 3.00 (2 H, d, J = 5 Hz), 3.73 (3 H, s), 3.90 (2 H, s), 6.61 (2 H, m), 7.03 (1 H, m).

The HCl salt was prepared by addition of anhydrous HCl to an ethereal solution of amine **23**. Recrystallization from 1-propanol afforded **23**·HCl: mp 261–262 °C dec (lit.[19] mp 261–262.5 °C); LC, flow rate 1.32 mL/min, $CHCl_3$, 250 × 3.2 mm column, Lichrosorb Si-60, 5 μm, t_R 9.9 min. Anal. Calcd for $C_{10}H_{14}NOCl$: C, 60.2; H, 7.1; N, 7.0. Found: C, 60.3; H, 7.1; N, 6.9.

The **8-methoxy-1,2,3,4-tetrahydroisoquinoline (23)** prepared above and the isomeric **6-methoxy-1,3,4-tetrahydroisoquinoline (24)** prepared as reported[9] from phenylethylamine **4** and formalin were clearly distinguished by GC (He, 160–165 °C, glass 6-ft U-tube, 5% Dexsil 300 on Anakrom Q): 8-isomer **23**, t_R = 14.8 min; 6-isomer **24**, t_R 17.0 min.

8-Methoxy-3,4-dihydroisoquinoline (22). A mixture of 200 mg (1.23 mmol) of **23** and 500 mg (5.75 mmol) of manganese dioxide[11a] in 10 mL of CH_2Cl_2 was stirred at 23 °C for 12 h, after which an additional 250 mg (2.87 mmol) of manganese dioxide was added. After a total of 40 h, the reaction mixture was filtered, and the filtrate was evaporated, affording 178 mg (1.10 mmol, 89%) of dihydroisoquinoline **22**, which was used without further purification. The 8-methoxyisoquinoline (**25**) impurity was present by NMR to <10%: NMR δ 8.6 (s, 1 H, CH=N), 6.5–7.3 (m, 3 H, Ar H), 3.8 (s, 3 H, OCH_3), 3.6 (t, J = 2 and 7.5 Hz, 2 H, NCH_2), 2.6 (t, 2 H, Ar CH_2).

1-(3,4-Dimethoxybenzyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2a). To a solution of 178 mg (1.10 mmol) of 8-methoxy-3,4-dihydroisoquinoline (**22**) in 5 mL of THF was added 16 mL (5.28 mmol, 0.33 M) of 3,4-dimethoxybenzylmagnesium chloride (**21**) in THF. After 10 h, the solvent was evaporated, the residue was acidified with 15 mL of 6 M hydrochloride acid and extracted with 4 × 8 mL of CH_2Cl_2, the combined organic extracts were washed, dried, and evaporated, and the residue was dissolved in 1-propanol and allowed to crystalize. There was obtained 170 mg (0.49 mmol, 44%) of isoquinoline hydrochloride **2a**: mp 218–219 °C after recrystallization from 1-propanol and pure by HPLC (see Table I): NMR δ 2.98 (4 H, m), 3.41 (2 H, d, J = 5 Hz), 3.68 (3 H, s), 3.80 (3 H, s), 3.83 (3 H, s), 5.03 (1 H, t, J = 5 Hz), 6.68 (5 H, m), 7.21 (1 H, m), 8.70 (2 H, br s). Anal. Calcd. for $C_{19}H_{24}NO_3Cl$: C, 65.2; H, 6.9; N, 4.0. Found: C, 65.4; H, 6.8; N, 4.0.

4-(Benzyloxy)benzyl Bromide (26e). 4-(Benzyloxy)benzyl alcohol (**26c**) in 100 mL ether was cooled to 0 °C, and 20 mL of 48% HBr was added. After 2 h of vigorous stirring, ice–water was added, the ether layer was separated, washed, dried, and evaporated, and the residue of **26e** was recrystallized from hexane: mp 81–82 °C; NMR δ 4.4 (s, 2 H, Ar CH_2Br), 5.0 (s, 2 H, OCH_2), 6.7–7.4 (m, 4 H, Ar H), 6.56 (s, 5 H, Ph). Anal. Calcd for $C_{14}H_{13}BrO$: C, 60.7; H, 4.7. Found: C, 61.0; H, 4.9.

1-Hydroxy-2-benzoyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (29). To a solution of 10 mL of CH_2Cl_2 and 0.33 g (2.0 mmol) of 8-methoxy-3,4-dihydroisoquinoline (**22**) prepared as described above, stirred under 4 mL of water in which KCN (0.523 g, 8.0 mmol, 400 mol %) was dissolved, was added benzoyl chloride (0.454 g, 4 mmol, 200 mol %) over a 2-h period. After further vigorous stirring for 6 h, the aqueous layer was separated and washed with 10 mL of CH_2Cl_2. The combined organic layers were washed, dried, and evaporated, and the resulting oil afforded crystalline **29** from ethanol: mp 150–152 °C; NMR δ 7.1–7.7 (m, 6 H, Ar H), 6.8–6.9 (m, 2 H, Ar H), 6.3 (very br, 1 H, C_1 H), 4.4 (very broad, 1 H, OH), 3.77 (s, 3 H, OCH_3), 3.1–4.0 (br, 2 H, C_3 H), 2.85 (m, 2 H, C_4 H). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1; N, 4.9. Found: C, 72.1; H, 6.6; N, 4.9.

2-Benzoyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (30a). To a solution of 1 g (6 mmol) of 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**23**) in 20 mL of pyridine at 0 °C was added 4 mL of benzoyl chloride over 2 h. After an additional 3 h at 0 °C, the solution was filtered, the filtrate was evaporated, and the remaining oil was taken up in CH_2Cl_2 and washed sequentially with 10 mL of 1 M NaOH, 2 × 10 mL of 10% HCl, and brine. The organic phase was then dried and evaporated to a solid, which was recrystallized from ethanol, yielding 1.21 g (4.5 mmol, 75%) of **30a**: mp 133–135 °C; NMR δ 7.4 (s, 5 H, Ar H), 6.5–7.3 (m, 3 H, Ar H), 4.6 (br s, 2 H, Ar CH_2N), 3.7 (s, 5 H, OCH_3, NCH_2), 2.8 (t, 2 H, Ar CH_2). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4; N, 5.2. Found: C, 76.4; H, 6.5; N, 5.2.

2-Pivaloyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (30c) was prepared using pivaloyl chloride and following the same procedure as described above for **30a**. Crude **30c** was crystallized from ligroin: mp 79–80 °C; NMR δ 1.28 [s, 9 H, $C(CH_3)_3$], 2.80 (br t, 2 H, Ar CH_2C), 3.8 (s, 3 H, OCH_3), 3.5–4.0 (m, 2 H, Ar CH_2C), 4.65 (s, 2 H, Ar CH_2N), 6.5–7.4 (m, 3 H, Ar H). High-resolution MS calcd for $C_{15}H_{21}NO_2$: 247.1572. Found: 247.1584.

2-(4-*tert*-Butylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (30b) was prepared using *p*-*tert*-butylbenzoyl chloride and following the same procedure as described above for **30a**. Crystallization from ether/hexane gave **30b**: mp 111–113 °C; NMR δ 1.33 [s, 9 H, $C(CH_3)_3$], 2.83 (br t, 2 H, Ar CH_2C), 3.75 (s, 3 H, OCH_3), 3.5–4.0 (m, 2 H, Ar CH_2C), 4.67 (br s, 2 H, Ar CH_2N), 6.5–7.2 (m, 3 H, Ar H), 7.37 (s, 4 H, benzoyl Ar H).

2-(4-Phenylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (30d). To a solution of 0.75 g (4.5 mmol) of 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**23**) in 2 mL of pyridine and

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25 mL of CH_2Cl_2 was added at 0 °C, over a period of 0.5 h, a solution of 4-phenylbenzoyl chloride (0.83 g, 5.0 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to 25 °C over 14 h. It was then evaporated, the residue was dissolved in 20 mL of CH_2Cl_2 and washed with 1 × 10 mL of 1 N NaOH and 2 × 10 mL of 10% HCl, and the organic phase was dried and evaporated to leave 750 mg of residue. Chromatography (SiO_2, 5% acetone/CH_2Cl_2) afforded **30d**, pure by HPLC (Lichrosorb, 60% hexane/40% $CHCl_3$): mp 171–173 °C (after crystallization from ethyl acetate); NMR δ 2.8 (t, J = 6 Hz, 2 H, Ar CH_2C), 3.73 (s, 3 H, OCH_3), 3.5–4.0 (m, 3 H, CCH_2N), 4.65 (br s, 2 H, Ar CH_2N), 6.5–7.7 (m, 12 H, Ar H). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.4; H, 6.2; N, 4.1. Found: C, 79.9; H, 6.2; N, 4.0.

1-[4-(Benzyloxy)benzyl]-2-(4-*tert*-butylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (33b). To a 70 mL of THF was added 0.40 mL (0.29 g, 2.86 mmol) of diisopropylamine, followed by *n*-BuLi (2,3 M, 1.13 mL, 2.60 mmol) at −70 °C. After the mixture was stirred for 0.5 h, 280 mg (0.87 mmol) of isoquinoline **30b** was added as a solution in 3 mL of THF over a 5-min period. After 2 h at −70 °C, 4-(benzyloxy)benzyl bromide (100 mol %, 240 mg, 0.87 mmol) was added as a solution in 2 mL of THF, and after 5 min, 2 mL of 2-propanol was added and the solution was allowed to warm to 0 °C. The reaction mixture was added to 50 mL of hexane and 50 mL of H_2O, the organic layer was washed with 20 mL of 1 N NaOH and 20 mL of brine, and the combined aqueous layers were backwashed with 40 mL of $CHCl_3$. The combined organic layers were dried and evaporated to yield an oil, which was subjected to preparative TLC (two 2-mm SiO_2 plates, 1:1 ether/hexane, each plate developed twice), and the major product was rechromatographed (SiO_2, 2:1 ether/hexane), yielding 138 mg (0.27 mmol, 31%) of **33b**, which was recrystallized from $CHCl_3$/hexane: mp 175–177 °C; NMR δ 1.26 [s, 9 H, $C(CH_3)_3$], 2.3–4.0 (m, 6 H), 3.8 (br s, 3 H, OCH_3), 4.9 (br s, 2 H, Ar OCH_2), 4.7-5.3 (m, 1 H, Ar CHN), 6.3–7.5 (m, 16 H, Ar H). Anal. Calcd for $C_{35}H_{37}NO_3 \cdot 0.5H_2O$: C, 79.4; H, 7.2; N, 2.6. Found: C, 79.6; H, 7.2; N, 2.6.

1-[4-(Benzyloxy)benzyl]-2-(4-phenylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (33d). A solution of 338 mg (0.98 mmol) of amide **30d** in 100 mL of dry THF was cooled to −70 °C and *tert*-butyllithium (1.05 M, 0.94 mL, 0.99 mmol, 100 mol %) was added dropwise, keeping the temperature below −65 °C. After 30 min at −70 °C, a solution of *p*-(benzyloxy)benzyl chloride (252 mg, 1.08 mmol, 110 mol %) in 5 mL of THF was added. The reaction mixture was allowed to warm to 0 °C over a 20-min period, at which time 2 mL of water was added, the solution was evaporated, and the residue was dissolved in 50 mL of ether and washed with 2 × 20 mL of H_2O and then 20 mL of brine. Drying and evaporating the organic phase left a residue, which was subjected to preparative TLC (four plates, 2-mm thick, SiO_2, eluting with 1.5% acetone in $CHCl_2$) and afforded a 20% recovery of educt **30d** and 325 mg (61% yield) of product **33d**: mp 146–147 °C (from ethyl acetate/hexane); NMR δ 2.5–3.2 (m, 2 H), 3.2–4.0 (m, 4 H), 3.75 (br s, 3 H, OCH_3), 4.6–5.3 (m, 3 H), 6.4–7.8 (m, 21 H, Ar H). Anal. Calcd. for $C_{37}H_{33}NO_3$: C, 82.3; H, 6.2; N, 2.6. Found: C, 82.0; H, 6.3; N, 2.6.

1-[4-(Benzyloxy)benzyl]-8-methoxy-1,2,3,4-tetrahydroisoquinoline (2c). To a solution of 200 mg (0.37 mmol) of **33d** in 75 mL of methanol was added 3.5 g of 3% sodium amalgam[20] in small chunks over 30 h. The reaction mixture was then filtered, and the filtrate was evaporated to an oil, which was taken up in CH_2Cl_2 and chromatographed on two preparative TLC plates (2 mm SiO_2, eluting with 10% methanol in CH_2Cl_2). The slowest band (R_f 0.5) consisted of the desired product **2c** (66 mg, 0.18 mmol, 50% yield): mp 94–96 °C (from ethyl acetate/hexane); NMR δ 1.74 (s, 1 H, NH), 2.4–3.5 (m, 6 H), 3.82 (s, 3 H, OCH_3), 4.32 (dd, J = 3 Hz, 10 H, Ar CHN), 5.02 (s, 2 H, OCH_2Ph), 6.5–7.5 (m, 12 H, Ar H). The HCl salt was crystallized from 1:1 ethanol/10% HCl: mp 178–179 °C. Anal. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.8; H, 6.6; N, 3.5. Found: C, 72.7; H, 6.7; N, 3.5.

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Registry No. 1a, 81625-16-3; **1a**·HCl, 4042-17-5; **1b**, 81625-17-4; **1b**·HCl, 81625-18-5; **1c**, 61273-84-5; **1c**·HCl, 81625-19-6; **2a**, 81625-20-9; **2a**·HCl, 81625-21-0; **2c**, 81625-22-1; **2c**·HCl, 81625-23-2; **3a**, 3979-58-6; **3c**, 76787-10-5; **4**, 2039-67-0; **5**, 591-31-1; **6**, 3179-09-7; **7**, 81625-24-3; **8a**, 93-40-3; **8c**, 6547-53-1; **9a**, 81625-25-4; **9c**, 76786-97-5; **9c**·HCl, 81625-26-5; **10**, 81625-27-6; **11**, 81625-28-7; **12**, 15184-99-3; **14**, 81625-29-8; **15**, 81625-30-1; **16**, 81625-31-2; **17**, 81625-32-3; **18**, 74904-29-3; **19**, 28281-58-5; **20**, 81625-33-4; **21**, 7306-46-9; **22**, 24693-44-5; **23**, 34146-68-4; **23**·HCl, 24693-40-1; **24**, 42923-77-3; **25**, 1723-70-2; **26c**, 836-43-1; **26d**, 836-42-0; **26e**, 5544-60-5; **26f**, 81625-34-5; **27**, 123-08-0; **27b**, 4397-53-9; **29**, 81625-35-6; **30a**, 81625-36-7; **30b**, 81625-37-8; **30c**, 81625-38-9; **30d**, 81625-39-0; **33b**, 81625-40-3; **33d**, 81625-41-4; pivaloyl chloride, 3282-30-2; *p*-*tert*-butylbenzoyl chloride, 1710-98-1; 4-phenylbenzoyl chloride, 14002-51-8.

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Enantiomeric α-Aminopropiophenones (Cathinone): Preparation and Investigation

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The preparation of the optical antipodes of α-aminopropiophenone (cathinone) from norephedrine and an improved large-scale resolution of norephedrine are described. The characterization of cathinone and its salts and their stability in various solvents are discussed.

The chewing of the leaves of *Catha edulis* Forsk (Khat) by the natives of several Asian and African countries to provide rapid stimulation is extremely prevalent[1] and has been considered to be a serious problem of drug dependence not unlike that associated with amphetamine.[2] In fact, on the basis of the observations of Eddy et al.,[3] the United Nations Narcotics Laboratory undertook research on the chemistry of Khat and its components.[2]

Earlier in this century (+)-norpseudoephedrine, a CNS-active compound, was identified among the basic alkaloid components of Khat.[4] Later investigations[5-8]

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