Congeners of the α Conformer of Dopamine Derived from Octahydrobenz[*h*]isoquinoline

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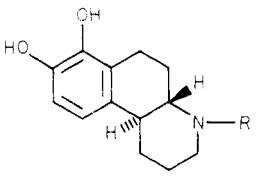
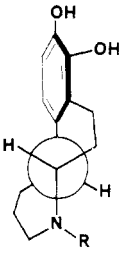
Two synthetic paths have been investigated for the preparation of cis and trans 8,9-dioxygenated octahydrobenz[*h*]isoquinoline ring systems. A sequence involving intramolecular Diels–Alder cyclization of a ring-opened intermediate product of a benzocyclobutene derivative was more satisfactory. The trans-fused isomers of the title compounds are frozen congeners of the α conformer of dopamine, isomeric with certain other tricyclic heterocycles which elicit a high degree of dopamine agonist activity. However, the present series of compounds exhibited a very low potency in an assay for dopamine-like actions. A possible reason for this inactivity has been suggested.

Prior communications[1a-d] from these laboratories have described high dopamine agonist potencies in a variety of animal test models of a series of *trans*-octahydrobenzo[*f*]quinoline derivatives **1**. In these molecules, the dop-



1, R = H, Me, Et, *n*-Pr



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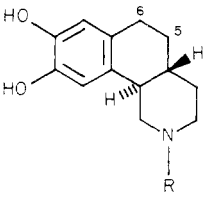

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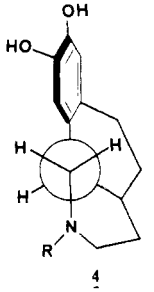
amine moiety is held rigidly in the so-called α conformer,[2] with the catechol ring and the amino group antiperiplanar and the "meta" OH on the edge of the ring nearer to the ethylamine side chain, as illustrated in the Newman projection **2**.

To investigate further the structure-activity relationships of dopamine agonists and to extend efforts to define the chemical and steric nature of some dopamine receptors, it was undertaken to incorporate the α conformer of dopamine into another rigid framework, the *trans*-8,9-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline **3**. Inspection of a Dreiding model of **3** indicates that the catechol ring deviates from coplanarity with the ethylamine side chain only by approximately 15°, as illustrated in **4**. It appears that the dopamine moiety in **3** coincides



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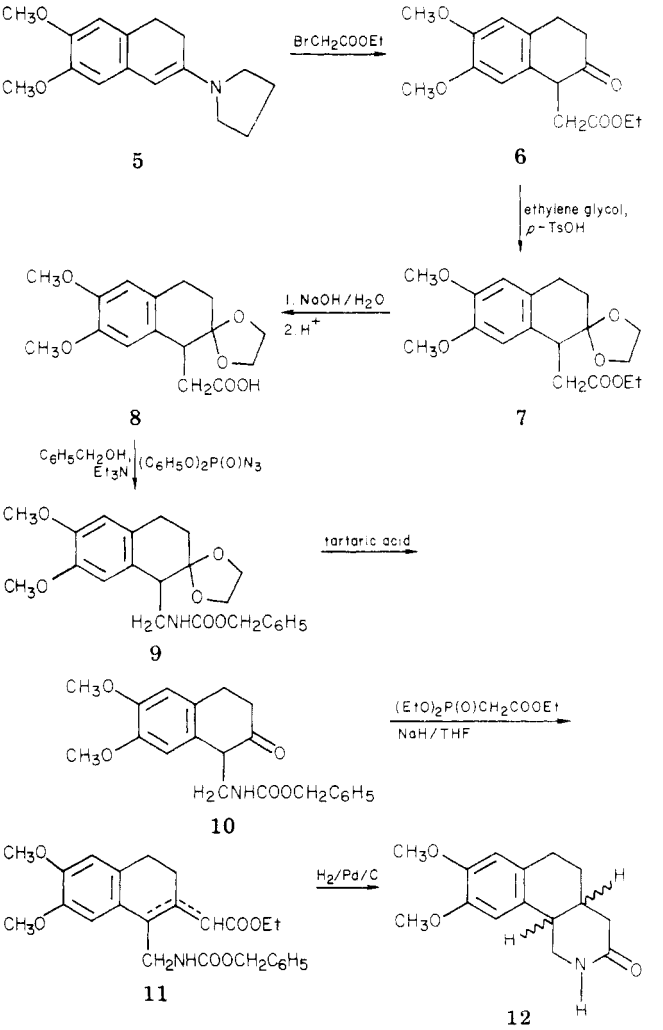
very closely with the proposed biologically active α conformer of dopamine.

Scheme I. Proposed Synthesis of the Octahydrobenz[*h*]isoquinoline Ring System



5 6 7 8 9 10 11 12

The initial approach to derivatives of **3** is illustrated in Scheme I. Reductive cyclization of **11** afforded a very small amount of **12**, whose mass spectrum was consistent with the proposed structure. Comparison of melting point data and NMR spectra of **12** with those of an authentic sample of the cis isomer of structure **12** (vide infra) suggested that the product isolated from the sequence in Scheme I was the *trans*-lactam. However, yields in the latter steps in this sequence were extremely poor and the products were very difficult to isolate and purify. Hence, an alternate route to the target system **3** was sought. Oppolzer[3] developed a synthetic sequence for the *cis*- and

(1) (a) Cannon, J. G.; Hatheway, G. J.; Long, J. P.; Sharabi, F. M. *J. Med. Chem.* **1976**, *19*, 987. (b) Sharabi, F. M.; Long, J. P.; Cannon, J. G.; Hatheway, G. J. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 630. (c) Sharabi, F. M.; Long, J. P.; Cannon, J. G. *Ibid.* **1977**, *202*, 97. (d) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341.

(2) Cannon, J. G. *Adv. Neurol.* **1975**, *9*, 177.

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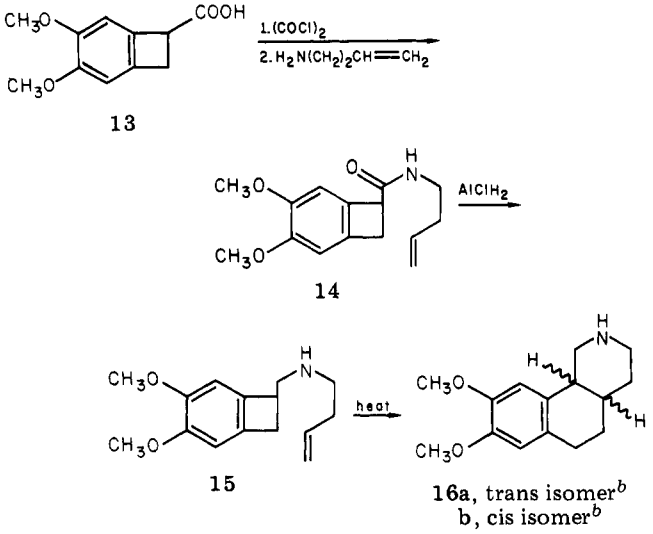
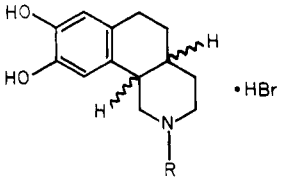
Scheme II. Oppolzer[a] Synthesis of *cis*- and *trans*-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz-[*h*]isoquinoline



[a] See ref 3. [b] Trans/cis ratio = 4:1.

Table I. Octahydrobenz[*h*]isoquinoline Derivatives



no.	ring fusion geometry	R	yield, %	mp, °C[a]	formula	anal.
3a	trans	H	93	280-282	$C_{13}H_{18}BrNO_2$	C, H, N
3b	trans	Me	72	289-291	$C_{14}H_{20}BrNO_2$	C, H, N
3c	trans	Et	94	269-271	$C_{15}H_{22}BrNO_2$	C, H, N
3d	trans	*n*-Pr	95	268-269	$C_{16}H_{24}BrNO_2$	C, H, N
21	cis	H	88	293-297	$C_{13}H_{18}BrNO_2$	C, H, N
22	cis	*n*-Pr	85	234-236	$C_{16}H_{24}BrNO_2$	C, H, N

[a] Recrystallized from MeOH-Et_2O.

trans-octahydrobenz[*h*]isoquinoline **16**, as illustrated in Scheme II. However, experimental details and some physical data for **16** and for certain intermediates remained unpublished at the time of the work described herein. Oppolzer specified use of AlH_3 in reduction of the amide **14**. In the present work, $AlClH_2$ (prepared from equimolar amounts of $LiAlH_4$ and $AlCl_3$) was found to be superior to $LiAlH_4$ for this reduction. The cis and trans isomers **16** were separable by fractional crystallization. The trans isomer was alkylated by standard methods, and the methyl ether protecting groups were removed with 48% HBr (see Table I).

Larger amounts of cis-fused octahydrobenz[*h*]isoquinolines were prepared, consistent with Oppolzer's strategy,[3] by procedures shown in Scheme III. The amide **18** could not be satisfactorily reduced to the secondary amine **15** (Scheme II) with $LiAlH_4$, $AlClH_2$, $NaBH_4$/AcOH, or "Red-Al". A modest amount of the unsaturated amine **15** was always accompanied by a sizeable amount of the saturated *N*-*n*-butylamine.

The cis secondary amine **20** (Scheme III) was converted to its *N*-*n*-propyl homologue, and ether links were cleaved with 48% HBr (see Table I).

(3) Oppolzer, W. *Synthesis* **1978**, 793.

Scheme III. Synthesis of *cis*-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline

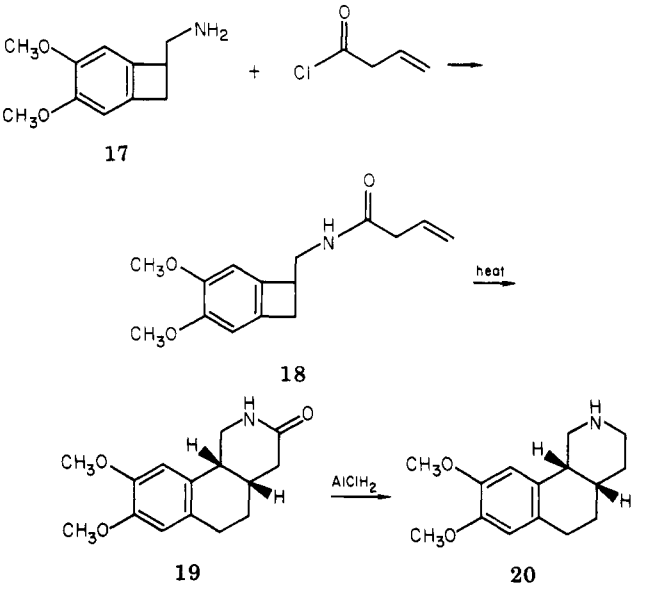


Table II. Cardioaccelerator Nerve Inhibition in the Cat

compd	ID_{50}, μmol/kg (95% CL), to antag of postgang cardioaccel stim in cats	inhibitory act. rel to apomorphine
3a	0.80 (0.4-5.6)[a]	0.027
3b	0.52 (0.3-1.8)	0.038
3c	0.81 (0.41-8.5)	0.025
3d	0.80 (0.5-2.1)	0.026
21	0.31 (0.16-0.6)	0.073
22	0.90 (0.35-2.3)	0.020
apomorphine	0.024 (0.02-0.03)	1.0

[a] These values were calculated from data obtained from at least five cats for each compound. Each cat received three cumulative doses of each compound. The doses were varied by 0.48 log intervals.

Pharmacology. Results and Discussion. Although the subject compounds are close structural analogues of the highly biologically active octahydrobenzo[*f*]quinoline systems **1**, a marked decrease (ca. 200×) in ability to inhibit sympathetic nerve transmission was observed (Table II). Two other differences were noted in comparing the isomeric systems **1** and **3**. Alkyl substitution on the amino group does not appear to alter the neural inhibitory activity of the octahydrobenz[*h*]isoquinolines, and the cis and trans isomers in this series were equally effective as inhibitors of cardioaccelerator nerve stimulation. In preceding experiments with the octahydrobenzo[*f*]quinolines **1**, it was demonstrated that the trans isomers were much more active than the cis isomers. In other respects, the inhibition of responses to neural stimulation, i.e., duration of effect and reversibility by haloperidol, appears similar to that found in the preceding studies.[1a-d]

One micromole per kilogram of the subject compounds administered intravenously lowered blood pressure and heart rate in anesthetized cats. The percentage reduction (±SE) in blood pressure observed was as follows: **3a**, 21.9 ± 6; **3b**, 14.6 ± 3.4; **3c**, 18.5 ± 5.8; **3d**, 13.3 ± 2.8; **21**, 27.9 ± 3.7; **22**, 31.7 ± 8.5. The beats/min reductions (±SE) in heart rate produced by the compounds (1 μmol/kg) were as follows: **3a**, 49 ± 1.0; **3b**, 3.2 ± 0.6; **3c**, 4.3 ± 0.6; **3d**, 3.0 ± 1.1; **21**, 13.6 ± 6.5; **22**, 21.6 ± 8.4. The reductions in heart rate and blood pressure were prevented by the

intravenous administration of haloperidol (100 μg/kg). Likewise, inhibition of cardioaccelerator nerve stimulation induced by the test compounds was prevented by the same doses of haloperidol.

Study of Dreiding models reveals that carbon-5 and -6 (structure 3) represent a bulky region in the octahydrobenz[*h*]isoquinoline molecule, not present in the molecules of potent dopamine agonists (dopamine itself, apomorphine, 2-aminotetralins, and octahydrobenzo[*f*]quinolines 1). It is possible that this area of molecular bulk prevents optimal interaction of the molecule 3 with dopamine receptor(s).

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-melt apparatus and are uncorrected. NMR spectra were recorded with a Varian Associates T-60 instrument using tetramethylsilane as the internal standard. IR spectra were recorded with a Perkin-Elmer 267 instrument. Mass spectra were recorded on a Finnigan 1015 S/L spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Pharmacology. Methods. Inhibition of Postganglionic Cardioaccelerator Nerve in Cats. The preparation involved induction of anesthesia by intrathoracic administration of sodium pentobarbital (30 mg/kg). The arterial pressure was measured from the right femoral artery using a Statham P23AA pressure transducer and was recorded using a Beckman RS dynograph. The pulses were integrated and recorded by use of a cardiotachometer. The respiration was supported by a Harvard respiratory pump and, following a midline incision of the thorax, bipolar platinum electrodes were placed on the right postganglionic cardioaccelerator nerves for stimulation using a Grass S4S stimulator. The frequency of stimulation was 2 Hz. The impulses were delivered for 20–30 s and a pulse duration of 5 ms was used. Supramaximal voltage was used. The experimental compounds were dissolved in 0.9% NaCl solution. Control volumes of normal saline solution larger than the volumes containing the experimental compounds did not alter the responsiveness of this preparation. The experimental procedure involved obtaining three reproducible positive chronotropic responses during stimulation of the right cardioaccelerator nerve. Following three consistent control responses, the compounds were administered in doses that varied by 0.48 log interval. At least three sequential and cumulative doses were used that bracketed the 50% inhibitory level. The amount of drug required to inhibit positive chronotropic responses by 50% was calculated.

Ethyl (1,2,3,4-Tetrahydro-2-oxo-6,7-dimethoxy-1-naphthyl)acetate (6). A solution of 6,7-dimethoxy-2-tetralone[4] (20 g, 0.098 mol) and 20.7 g (0.29 mol) of freshly distilled pyrrolidine in 200 mL of dry benzene was refluxed in a Dean–Stark apparatus under N_2 for 5 h. Benzene and excess pyrrolidine were removed under reduced pressure, and the residue was maintained at vacuum pump pressure at room temperature overnight. The solid enamine 5 was dissolved in 80 mL of dry benzene, and 17.8 g (0.11 mol) of ethyl bromoacetate in 20 mL of dry benzene was added dropwise under N_2 at room temperature with stirring. Then, the reaction mixture was heated under reflux for 3 h. The reaction solution was cooled and was stirred for 1 h with 80 mL of H_2O. The organic layer was then separated and the aqueous phase was washed once with benzene. The pooled organic layers were washed with H_2O and dried ($MgSO_4$), and volatiles were removed under reduced pressure (first aspirator and then vacuum pump) to afford an oily brown residue. This was chromatographed on silica gel and eluted with $CHCl_3$ to give an oil, which was fractionally distilled to yield 5 g of 6,7-dimethoxy-2-tetralone, bp 165–180 °C (0.07 mm), and 13.7 g (65%) of 6, bp 185–192 °C (0.07 mm), which crystallized upon standing at room temperature, mp 72–73 °C. Anal. ($C_{16}H_{20}O_5$) C, H.

Ethyl [1,2,3,4-Tetrahydro-2,2-(ethylenedioxy)-6,7-dimethoxy-1-naphthyl]acetate (7). A solution of 3.4 g (0.0116 mol) of 6, 0.840 g (0.0135 mol) of ethylene glycol, and a catalytic amount of *p*-TsOH in 50 mL of dry benzene was refluxed for 3 h in a Dean–Stark apparatus. The resulting mixture was then washed with saturated $NaHCO_3$ solution and H_2O and dried ($MgSO_4$). The solvent was evaporated to leave an oil, which was crystallized from cyclohexane to afford 3.7 g (95%) of a crystalline solid, mp 99–101 °C. Anal. ($C_{18}H_{24}O_6$) C, H.

[1,2,3,4-Tetrahydro-2,2-(ethylenedioxy)-6,7-dimethoxy-1-naphthyl]acetic Acid (8). A mixture of 2.5 g (0.00743 mol) of 7, 15 mL of 60% aqueous NaOH, and 15 mL of 95% EtOH was heated under reflux for 20 h. The reaction mixture was then treated with 100 mL of saturated NaCl and was washed with Et_2O. The aqueous solution was then cooled in an ice bath, acidified with cold 6 N HCl, and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated NaCl, dried ($MgSO_4$), and evaporated to afford a brown residue, which was recrystallized from benzene to give 2.1 g (92%) of product, mp 146–148 °C. Anal. ($C_{16}H_{20}O_6$) C, H.

Benzyl *N*-[[1,2,3,4-Tetrahydro-2,2-(ethylenedioxy)-6,7-dimethoxy-1-naphthyl]methyl]carbamate (9). A mixture of 1.6 g (0.00519 mol) of 8, 1.43 g (0.00520 mol) of diphenyl phosphoryl azide, and 0.572 g (0.00565 mol) of triethylamine in 12 mL of benzene was refluxed under N_2 for 45 min. Benzyl alcohol (0.6 g, 0.00555 mol) was added and the mixture was refluxed for 18 h. The cooled reaction mixture was washed with 5% aqueous citric acid, H_2O, saturated $NaHCO_3$ and saturated NaCl. The organic layer was dried ($MgSO_4$) and evaporated to leave an oil, which was chromatographed on silica gel and eluted with $CHCl_3$–EtOAc (20:1) to give 2.1 g of material containing 9 contaminated with another component. This material was chromatographed on alumina and eluted with $CHCl_3$–hexane (5:2) to give a major fraction, which was again chromatographed on silica gel and eluted with $CHCl_3$–EtOAc (20:1) to afford 1.1 g (51%) of 9: IR (neat) 1710 (C=O), 3420 cm^{-1} (br, NH); NMR ($CDCl_3$) δ 1.68–2.02 (m, 2 H, $PhCH_2CH_2$–), 2.82 (t, 2 H, benzylic H), 3.00 (t, 1 H, methine H), 3.50 (d, 2 H, CH_2NH), 3.77 (s, 6 H, OCH_3), 3.93 (s, 4 H, $-OCH_2CH_2O$–), 5.02 (s, 2 H, CH_2Ph), 5.43 (br s, 1 H, NH), 6.47, 6.62 (s, 2 H, arom), 7.23 (s, 5 H, arom); MS *m/e* 413 (M^+).

Benzyl *N*-[[1,2,3,4-Tetrahydro-2-oxo-6,7-dimethoxy-1-naphthyl]methyl]carbamate (10). A mixture of 1.1 g (0.0026 mol) of 9 and 25 mL of saturated aqueous tartaric acid solution was stirred at room temperature for 24 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, saturated $NaHCO_3$, and H_2O and was dried ($MgSO_4$). The solvent was evaporated to give 0.6 g (63%) of an oil: IR (neat) 1710 cm^{-1} (C=O); MS *m/e* 369 (M^+).

3-Oxo-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline (12). To a suspension of 0.094 g (0.00195 mol) of NaH (50% in mineral oil) in 5 mL of dry tetrahydrofuran was added a solution of 0.0437 g (0.00195 mol) of triethyl phosphonoacetate in 3 mL of dry tetrahydrofuran under N_2 and at 0 °C. After the addition was complete, stirring was continued in the cold for 30 min, and then 0.7 g (0.00195 mol) of 10 in 3 mL of dry tetrahydrofuran was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 3 h and finally was heated under reflux for 30 min. The cooled reaction mixture was quenched with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried ($MgSO_4$), and evaporated to give a semisolid, which was chromatographed on silica gel and eluted with $CHCl_3$–EtOAc (20:1). The eluate provided ca. 0.1 g of an oil, which was hydrogenated in 50 mL of MeOH over 0.05 g of 5% Pd/C at an initial pressure of 50 psig for 24 h. The reduction mixture was filtered and treated with anhydrous NH_3 for 1 h, and the volatiles were removed under reduced pressure. The residue was recrystallized from $CHCl_3$–Et_2O to afford 0.025 g of a crystalline product: mp 192–194 °C; IR (KBr) 1660 cm^{-1} (lactam C=O); MS *m/e* 261 (M^+).

***N*-(3-Butenyl)-4,5-dimethoxybenzocyclobutene-1-carboxamide (14).** 4,5-Dimethoxybenzocyclobutene-1-carboxylic acid[5] (1.5 g, 0.0072 mol) and 1.5 g (0.012 mol) of oxalyl chloride in 3

(4) Cannon, J. G.; Lee, T.; Goldman, H. D.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1977**, *20*, 1111.

(5) Kametani, T. *Tetrahedron* **1973**, *29*, 73.

mL of benzene was stirred at room temperature for 2 h. The mixture was then diluted with benzene and was evaporated to leave a yellow solid. Addition of benzene and evaporation were repeated twice more. The acid chloride was taken up in 2 mL of CH_2Cl_2, and 2 mL of dry pyridine was added. The resulting solution was cooled to -15 °C, and 0.62 g (0.00865 mol) of 3-butenylamine[6] in 2 mL of CH_2Cl_2 was added dropwise. The reaction mixture was then stirred at room temperature for 1 h. It was diluted with 50 mL of CH_2Cl_2 and washed with cold saturated NaCl solution, dilute HCl, and 5% $NaHCO_3$ solution. Upon evaporation of the CH_2Cl_2, a yellow solid remained, which was recrystallized from CH_2Cl_2–Et_2O to afford 1.15 g (65%) of a pale yellow powder: mp 110-112 °C; MS *m/e* 261 (M^+). Anal. ($C_{15}H_{19}NO_3$) C, H, N.

***N*-(3-Butenyl)-4,5-dimethoxybenzocyclobutenylmethylamine Hydrochloride (15).** To an ice-cooled suspension of $LiAlH_4$ (0.52 g, 0.013 mol) in 10 mL of dry Et_2O was added 1.74 g (0.013 mol) of $AlCl_3$ in 10 mL of dry Et_2O, under N_2. After 0.25 h, 1.7 g (0.0065 mol) of **14** was added in portions. Then, the ice bath was removed and the reaction mixture was stirred for 2 h. The reaction was then quenched by cautious addition of dilute HCl. The resulting cloudy aqueous solution was basified with NaOH and was extracted twice with $CHCl_3$. Evaporation of the pooled extracts gave a yellow oil, which was treated with ethereal HCl. The resulting salt was recrystallized from MeOH–Et_2O to give 1.4 g (76%) of a light tan solid: mp 186–188 °C; MS *m/e* 247 (M^+).

8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline Hydrochloride, Cis and Trans Isomers 16a,b. The free amine from 1.4 g (0.0057 mol) of **15** in 125 mL of *o*-dichlorobenzene was heated under reflux for 18 h. The cooled brown solution was acidified with ethereal HCl, and the volatiles were evaporated. The residue was fractionally crystallized from MeOH–Et_2O to give 0.819 g (59%) of the trans isomer **16a**, mp 249–252 °C (lit.[3] mp 249–252 °C), and 0.172 g (12%) of the cis isomer **16b**, mp 209–211 °C: MS of trans isomer, *m/e* 247 (M^+); of cis isomer, *m/e* 247 (M^+).

***trans*-*N*-*n*-Propyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline Hydrochloride (23).** Using the method of Marchini et al.,[7] the free base isolated from 0.3 g (0.00106 mol) of **16a** was alkylated with 1.33 g (0.018 mol) of propionic acid and 0.202 g (0.0053 mol) of $NaBH_4$ in 30 mL of dry benzene. The light yellow oily product was converted to its HCl salt and this was recrystallized from MeOH–Et_2O to give 0.284 g (83%) of product: mp 216–218 °C; MS *m/e* 289 (M^+ of free base).

***trans*-*N*-Ethyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline Hydrochloride (24).** Using the method of Marchini et al.,[7] the free base isolated from 0.26 g (0.00917 mol) of **16a** was alkylated with 0.936 g (0.0156 mol) of AcOH and 0.175 g (0.0046 mol) of $NaBH_4$ in 30 mL of dry benzene. The pale yellow oily product was converted to its HCl salt and this was recrystallized from MeOH–Et_2O to give 0.246 g (86%) of product: mp 257–259 °C; MS *m/e* 275 (M^+ of free base).

***trans*-*N*-Methyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline Hydrochloride (25).** A mixture of 0.260 g (0.00917 mol) of **16a**, 0.5 mL of 37% aqueous formaldehyde (0.005 mol), and 0.126 g (0.002 mol) of $NaCNBH_3$ in 5 mL of MeOH was stirred at room temperature overnight; AcOH was added from time to time to maintain pH ca. 7.0 (pH paper). Following the workup procedure of Borch et al.,[8] 0.226 g (83%) of the product was obtained: mp 250–252 °C; MS *m/e* 261 (M^+ of free base).

***N*-[(4,5-Dimethoxybenzocyclobutenyl)methyl]-3-butenamide (18).** 1-(Aminomethyl)-4,5-dimethoxybenzocyclobutene[9] (from 4.59 g, 0.020 mol, of the HCl salt), 3-butenoyl chloride (2.4 g, 0.023 mol), and 5 mL of pyridine in 30 mL of CH_2Cl_2 were treated according to a method of Oppolzer.[3] The crude product was chromatographed on silica gel and eluted with CH_2Cl_2–Me_2CO (9:1) to give an oil, which was recrystallized from CH_2Cl_2–Et_2O to afford a pale yellow crystalline solid (1.536 g, 29%), mp 109–111 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

***cis*-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinolin-3-one (19).** Compound **18** (0.56 g, 0.002 mol) in 26 mL of *o*-dichlorobenzene was heated under reflux for 18 h. Volatiles were removed under reduced pressure and the oily residue slowly solidified. It was recrystallized from Me_2CO–Et_2O to afford 0.32 g (57%) of a tan solid, mp 163–166 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

***cis*-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline Hydrochloride (20).** To an ice-cooled suspension of 0.256 g (0.0064 mol) of $LiAlH_4$ in dry Et_2O was added under N_2 a solution of 0.854 g (0.0064 mol) of $AlCl_3$ in 10 mL of dry Et_2O. After 0.25 h, 0.557 g (0.00213 mol) of **19** was added and the mixture was stirred at room temperature for 2.25 h. Excess dilute HCl was cautiously added and the aqueous solution was washed with Et_2O, basified with NaOH, and extracted twice with $CHCl_3$. Evaporation of the $CHCl_3$ gave an oil, which was converted to its HCl salt with ethereal HCl. Recrystallization from MeOH–Et_2O gave 0.35 g (66%) of small light tan needles: mp 210–213 °C; MS *m/e* 217 (M^+ of free base). Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

***cis*-*N*-*n*-Propyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenz[*h*]isoquinoline Hydrochloride (26).** Using the procedure of Marchini et al.,[7] the free base from 0.177 g (0.000624 mol) of **20** was alkylated with 0.119 g (0.00312 mol) of $NaBH_4$ and 0.785 g (0.0106 mol) of propionic acid in 15 mL of dry benzene. The yellow oily product was converted to its HCl salt and this was recrystallized from MeOH–Et_2O to yield 0.118 g (58%) of short needles: mp 244–246 °C; MS *m/e* 289 (M^+ of free base). Anal. ($C_{18}H_{28}ClNO_2$) C, H, N.

Ether Cleavage Reactions. The amine hydrochloride (0.001 mol) was heated in 30 mL of 48% HBr under N_2 at 135–145 °C for 3 h. Volatiles were removed under reduced pressure and the residue was recrystallized (see Table I).

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