Synthesis and Biological Evaluation of a Tetrahydroisoquinoline Derivative Possessing Selective β_2-Adrenergic Agonist Activity

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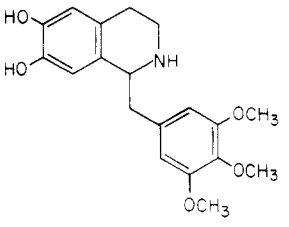
This paper reports the synthesis of 4-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (2) and 2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine (3). The biological activity of these agents relative to that of trimetoquinol (1) in guinea pig atria and guinea pig trachea is reported. The relative activities in relaxation of guinea pig trachea is 1 > 2 > 3 while in the chronotropic response in guinea pig atria the relative order of activity is 1 > 3 >> 2.

Tetrahydroisoquinolines, which may be characterized as cyclized β-phenethylamines, have been shown to possess either agonist or antagonist activity in a variety of adrenoceptor systems.[2-5] Of the tetrahydroisoquinoline class, trimetoquinol [1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline] (1) has been reported to be the most potent β-adrenoceptor agonist.[2-8] Originally reported to be selective for the β-adrenoceptor systems of trachea (β_2) vs. atria (β_1),[9,10] recent evidence has indicated that trimetoquinol is a nonselective β-stimulant.[11,12] In a continuation of our investigations to alter the structure of trimetoquinol in order to develop more selective and/or potent β_2-stimulants, we report the synthesis and biological evaluation of 4-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (2) and 2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine (3). In both of these compounds, the arylmethyl group positionally corresponds to the β-hydroxyl group of phenethanolamines. It has been suggested that the arylmethyl group of 1 may compensate for the β-hydroxyl group of phenethanolamines to facilitate proper alignment and binding of trimetoquinol to the β-adrenoceptor.[8,13]



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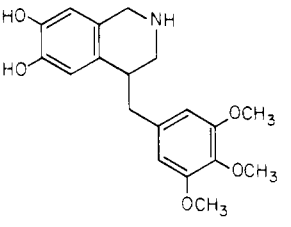

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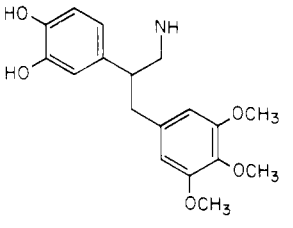
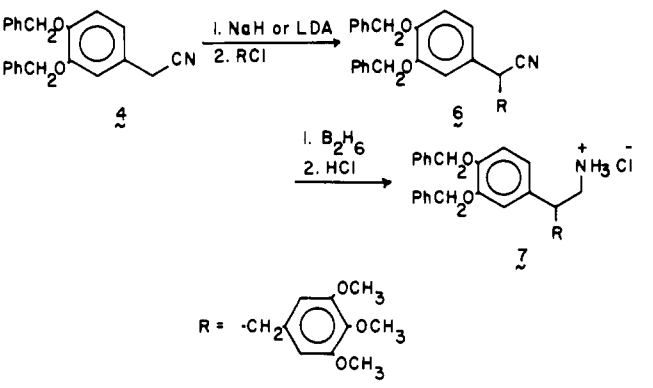


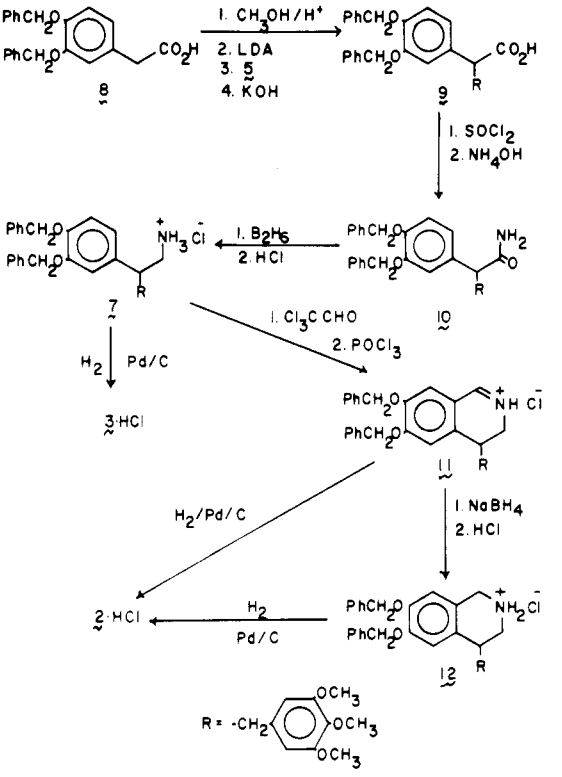
3

Chemistry. Both the 4-substituted analogue 2 and the norepinephrine analogue 3 were prepared from the intermediate 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine (7) (see Scheme I). The amine 7 was prepared by alkylating 3,4-dibenzyloxyphenylacetonitrile (4)[14] with 3,4,5-trimethoxybenzyl chloride (5). Alkylation of nitrile 4 using sodium hydride in DMF[15] yielded the monoalkylated product, 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (6), along with dialkylated product and starting material while alkylation with lithium diisopropylamide (LDA)[16] in THF and hexamethylphosphoramide (HMPA) yielded only monoalkylated product and starting material. Reduction

Scheme I



Scheme II



of nitrile 6 with diborane in THF afforded 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine (7) isolated as the hydrochloride salt.

Amine 7 could also be obtained from 3,4-dibenzyloxyphenylacetic acid[14] (8) (see Scheme II). Esterification of acid 8, followed by alkylation with LDA in THF and HMPA and hydrolysis, yielded α-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid (9). Conversion of acid 9 to the acid chloride followed by treatment of the acid chloride with ammonium hydroxide yielded α-

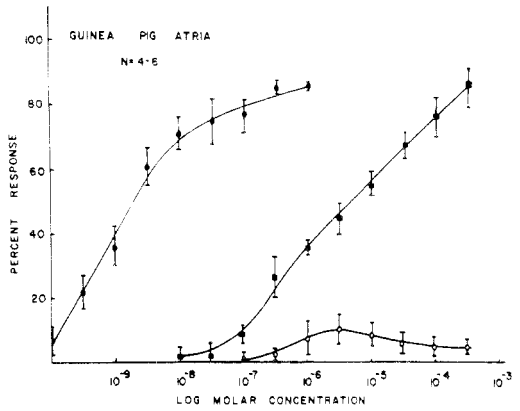


Figure 1. Log dose–response curves for *dl*-trimetoquinol (1) and analogues 2 and 3 on tracheal preparations: *dl*-trimetoquinol (●—●); analogue 2 (○—○); and analogue 3 (■—■). Values plotted represent the mean ± SE of N = 4–6.

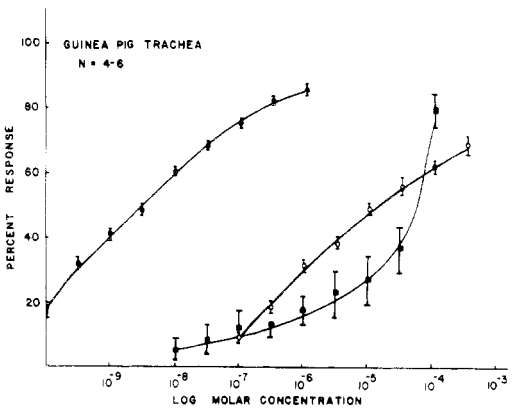


Figure 2. Log dose–response curves for *dl*-trimetoquinol (1) and analogues 2 and 3 on guinea pig atrial preparations: *dl*-trimetoquinol (●—●); analogue 2 (○—○); and analogue 3 (■—■). Values plotted represent the mean ± SE of N = 4–6.

(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid amide (**10**). The amide was reduced with diborane in THF to yield the amine **7**.

Hydrogenolysis of amine **7** using 10% palladium on charcoal afforded the catechol **3**·HCl.

Formylation of amine **7** with chloral in chloroform and triethylamine[17] followed by cyclization of the crude *N*-formyl intermediate by stirring in phosphorus oxychloride at 0–4 °C gave the desired imine **11**, which could be isolated from the reaction mixture as the hydrochloride salt. Evidence for cyclization to 6,7-dibenzyloxy-4-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline hydrochloride rather than to 7,8-dibenzyloxy-4-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline hydrochloride may be found in the NMR spectrum. A spectrum of the free base of **11** in deuterated chloroform shows two aromatic protons at positions 5 and 8 of the dihydroisoquinoline ring appearing as two singlets at δ 6.43 and 6.93. The proton in the 1 position appears as a broad singlet at δ 8.25. In a spectrum of the hydrochloride **11** in deuterated chloroform, the aromatic protons appear as singlets at δ 6.62 and 7.68, and the proton at the 1 position appears as a broad singlet at δ 9.18.

Reduction of the imine **11** with sodium borohydride in methanol yielded 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline (**12**) isolated as the hydrochloride salt. Removal of the benzyloxy-protecting groups using catalytic hydrogenation with 10% palladium on charcoal yielded catechol **2**·HCl. More directly, **2**·HCl could be obtained by catalytic hydrogenation with 10% palladium on charcoal of the imine hydrochloride **11**.

Results and Discussion

Compounds **2** and **3** were evaluated pharmacologically in the isolated β-adrenoceptor systems of guinea pig trachea and atria. The relative abilities of the 4-substituted analogue **2** and the norepinephrine analogue **3** to produce chronotropic response and tracheal relaxation are illustrated in Figures 1 and 2, respectively. It is clear that shifting the 1-arylmethyl group to the appropriate position resulted in compounds **2** and **3** possessing smaller pD_2 values than the parent compound *dl*-trimetoquinol (**2**). Compound **3**, which does not contain an intact tetrahydroisoquinoline ring system and may be visualized as a β-substituted norepinephrine analogue, possessed a greater potency in the atrial preparation than **2**.

Interestingly, the 4-substituted tetrahydroisoquinoline **2** was essentially inactive in eliciting a chronotropic response in the isolated guinea pig atrial preparation and able to produce a significant relaxation of tracheal muscle ($ED_{50} \simeq 10^{-5}$ M). Although **2** is considerably less active than **1** in tracheal relaxation, it possesses selectivity for stimulation of this β-adrenoceptor system (see Figures 1 and 2).

β-Adrenoceptor systems have been subclassified as β_1 (lipolysis, heart muscle) and β_2 (trachea) types. In earlier reports[2a,3,5] we have found that fragmentation of the intact tetrahydroisoquinoline nucleus of **1** between (a) the 4-carbon atom and catechol ring or (b) 1-carbon atom and catechol ring leads to analogues with reduced β-adrenoceptor activity; in addition, no selective action of these analogues on adrenoceptor systems was observed. Similarly, in the present study, the fragmented analogue **3** was considerably less active as compared to **1** in both β_1- and β_2-adrenoceptor systems. However, a retention of an intact tetrahydroisoquinoline ring system of **3** gave an analogue **2** which exhibited a selective action on β_2-adrenoceptors (trachea vs. heart muscle).

Few studies have examined the influence of substitution in the tetrahydroisoquinoline nucleus on the pharmacological activity of **1** or related analogues. Iwasawa and Kiyomoto[8] reported that alkyl substitution in the tetrahydroisoquinoline ring reduced the β-adrenoceptor properties of the parent molecule. Analogue **2** differs from **1** only in the placement of the 3,4,5-trimethoxybenzyl group in the tetrahydroisoquinoline nucleus and can be classified chemically as a 4-substituted 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline. In this regard, 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and the closely related analogue, salsolinol, have previously been shown to possess little adrenoceptor activity.[12] It is clear that substitution of a 3,4,5-trimethoxybenzyl group at the 4 position of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline leads to an analogue with selective β_2-adrenoceptor activity. Thus, it would appear that a further investigation of the β-adrenoceptor properties of 4-arylalkyl or 4-alkyl analogues of **1** or related analogues is warranted.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Perkin-Elmer 237 infrared spectrophotometer, a Beckmann 4230 infrared spectrophotometer, a Varian A-60A nuclear magnetic resonance spectrophotometer at 60 MHz or a Bruker HX 90E nuclear magnetic resonance spectrometer at 90 MHz, and a Du Pont Model 491 mass spectrometer.

2-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)-propionitrile (6). In a three-necked 250-mL round-bottom flask under argon and cooled in an ice bath was generated in situ lithium diisopropylamide (LDA) by adding 9.5 mL of 1 M *n*-butyllithium

to 1.55 g of diisopropylamine. After 20 min the solution was cooled to −78 °C with a dry ice–acetone bath and 5.00 g (15.2 mmol) of nitrile **4** dissolved in 50 mL of freshly distilled THF was added with stirring. After 2.75 h 3.30 g of 3,4,5-trimethoxybenzyl chloride (**5**) dissolved in 30 mL of THF and 0.6 g of hexamethylphosphoramide (HMPA) was added and the reaction mixture was allowed to go to room temperature. After 3 h 5% aqueous hydrochloric acid was added and the product was extracted with Et_2O. The ethereal layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was redissolved in Et_2O and allowed to slowly evaporate to yield 3.44 g (44.7%) of **6**, mp 99 °C.

2-(3,4-Dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine Hydrochloride (7). Method A. Under an argon atmosphere was refluxed 3.00 g (5.89 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)propionitrile (**6**) in 150 mL of THF and 25 mL of 1 M diborane. After 24 h the solution was cooled and excess diborane was carefully decomposed with 10% aqueous potassium hydroxide. The mixture was then acidified with 10% aqueous hydrochloric acid and stirred at room temperature for several hours. The mixture was again made basic and extracted with Et_2O and chloroform. The organic layers were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was redissolved in ca. 50 mL of Et_2O and 10 mL of anhydrous ethanol. Et_2O saturated with anhydrous hydrogen chloride was then added with stirring. The resulting gum was azeotroped with isopropyl alcohol and recrystallized from ethanol–Et_2O to yield 2.73 g (84.3%) of the hydrochloride salt **7**, mp 130 °C.

Method B. To 1.20 g (2.35 mmol) of 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid amide (**10**) dissolved in 100 mL of THF was added 15 mL of 0.9 M diborane. After refluxing under argon for 3 h the solution was cooled and acidified with Et_2O saturated with anhydrous hydrogen chloride gas. After stirring for 1 h the solution was made basic with 10% aqueous potassium hydroxide solution and extracted with chloroform. After drying over $MgSO_4$ and filtration, the chloroform was removed in vacuo. The residue was dissolved in 100 mL of Et_2O containing ca. 5 mL of ethanol and Et_2O saturated with anhydrous hydrogen chloride gas was added to yield 0.57 g (44.0%) of the hydrochloride salt **7**, mp 130 °C.

3,4-Dibenzyloxyphenylacetic Acid (8). In a 100-mL round-bottom flask 6.00 g (18.2 mmol) of 3,4-dibenzyloxybenzyl nitrile (**4**) was refluxed for 24 h in a solution containing 30 mL of methanol, 20 mL of dioxane, 10 g of potassium hydroxide, and 10 mL of water. After in vacuo removal of solvent Et_2O was added to the mixture and the acid was extracted with a saturated aqueous sodium bicarbonate solution. After acidification of the bicarbonate solution with dilute hydrochloric acid and extraction with Et_2O, the product was dried over magnesium sulfate. Upon filtration and removal of solvent 4.74 g of crude acid was obtained. Upon recrystallization from Et_2O–pentane 4.38 g (**8**) (69.0%) of white needles, mp 107 °C, was obtained (lit.[14] mp 109 °C from acetone–cyclohexane).

α-(3,4,5-Trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic Acid (9). The 3,4-dibenzyloxyphenylacetic acid was quantitatively esterified by stirring for 24 h in a large excess of anhydrous methanol containing several drops of concentrated hydrochloric acid. After in vacuo removal of excess methanol the product was dissolved in Et_2O, washed with saturated aqueous bicarbonate solution and saturated aqueous sodium chloride solution, and dried over magnesium sulfate. After filtration and concentration of the ethereal solution creamy white crystals of the methyl ester, mp 41–42 °C [lit. reported as oil, bp 189–190 °C (0.9 mm)], were obtained upon freezing in a dry ice–acetone bath.

Lithium diisopropylamide was generated in situ in a 100-mL three-necked round-bottom flask under argon and cooled in an ice bath by adding to 1.12 g (11.0 mmol) of diisopropylamine in 5 mL of THF 8.3 mL of 1.67 M *n*-butyllithium in hexane. The mixture was then cooled 30 min in a methanol–ice bath (−40 °C). To the mixture was added 4.00 g (11.0 mmol) of methyl 3,4-dibenzyloxyphenylacetate dissolved in 11 mL of THF. One hour later 2.40 g (11.1 mmol) of 3,4,5-trimethoxylbenzyl chloride (**5**) dissolved in 0.66 g of HMPA and 10 mL of THF was added and stirring was continued for 2 h. Et_2O was added to the mixture and the solution was washed with 10% aqueous hydrochloric acid, saturated aqueous bicarbonate solution, and saturated aqueous sodium chloride solution and dried over $MgSO_4$. After filtration the solvent was removed in vacuo and the residue was dissolved in 50 mL of anhydrous Et_2O. Upon slow evaporation 5.30 g (88.4%) of methyl 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetate, mp 80–81 °C, was obtained. Upon recrystallization from ethyl ether–hexane, ester product, mp 93–94 °C, was obtained. To a 1-L round-bottom flask was added 2.97 g (5.48 mmol) of methyl 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetate, 10 g of potassium hydroxide, and 700 mL of 95% ethanol. After refluxing for 24 h the solvent was removed and the product dissolved in water. The aqueous solution was washed with Et_2O, acidified with dilute hydrochloric acid, and extracted with Et_2O. The ether layer was washed with saturated aqueous sodium chloride and dried over $MgSO_4$. After filtration the Et_2O was slowly evaporated to give a powdery white product. Recrystallization from $CHCl_3$–Et_2O–pentane yielded 2.58 g (89.1%) of the acid **9**, mp 104–105 °C.

α-(3,4,5-Trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic Acid Amide (10). To a 100-mL round-bottom flask containing 1.00 g (1.89 mmol) of 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid (**9**) was added 2 mL of thionyl chloride. After stirring for 15 min at room temperature excess thionyl chloride was removed in vacuo and the acid chloride formed [IR (NaCl, neat) 1760 cm^{-1}] was dissolved in 25 mL of Et_2O. The ethereal solution was then added to 50 mL of concentrated ammonium hydroxide and allowed to evaporate overnight. The remaining precipitate was filtered, washed with water and ethyl ether, and recrystallized from chloroform–Et_2O to give 0.79 g (79.0%) of **10**, mp 106–108 °C.

2-(3,4-Dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propylamine Hydrochloride (3). 2-(3,4-Dibenzyloxyphenyl)-3,4,5-(trimethoxyphenyl)propylamine hydrochloride (1.80 g, 3.27 mmol) dissolved in 400 mL of absolute ethanol was hydrogenated at 40 psi for 24 h with 0.2 g of 10% Pd/C catalyst. After vacuum filtration through a Celite padded filter, removal of solvent, and recrystallization from ethanol–Et_2O, 906 mg (74.9%) of **3**, mp 213–214 °C, was isolated.

4-(3,4,5-Trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinoline Hydrochloride (11). To an ice-cooled 50-mL round-bottom flask were added 1.00 g (1.82 mmol) of 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (**7**), 2 mL of triethylamine, and 0.37 g of chloral dissolved in 5 mL of chloroform. After stirring for 20 min the mixture was refluxed for 1 min and evaporated in vacuo. The residue was dissolved in Et_2O and filtered to remove triethylamine hydrochloride formed in the reaction. The ethereal layer was again evaporated in vacuo to yield a crude *N*-formyl intermediate as an oil: IR (NaCl, neat) 1675 cm^{-1} (*N*-formyl). This intermediate was dissolved in 15 mL of phosphorus oxychloride and stirred at 4 °C for 1 h. The phosphorus oxychloride was removed in vacuo and the residue was washed with 10% aqueous potassium hydroxide and extracted with chloroform. After drying over $MgSO_4$ and filtering, the chloroform solution was concentrated in vacuo to ca. 5 mL. Et_2O saturated with anhydrous hydrogen chlorine gas was added to the chloroform solution and the desired product **11** was crystallized from the reaction mixture through equilibration in a saturated ethyl ether chamber. The yellow-opaque crystalline product was recrystallized from methanol–Et_2O to give 460 mg (45.2%) of a light yellow crystalline **11**, mp 205–206 °C.

4-(3,4,5-Trimethoxybenzyl)-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline (12). In a 250-mL round-bottom flask was dissolved with heating 300 mg (0.54 mmol) of 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinoline (**11**) in 100 mL of methanol. To the cooled solution was added 500 mg of sodium borohydride and the solution was stirred for 3 h. The solvent was removed in vacuo, water was added, and the product was extracted with chloroform. The chloroform solution was dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was dissolved in Et_2O and converted to the hydrochloride salt by the addition of Et_2O saturated with anhydrous hydrogen chloride gas. Recrystallization from methanol–Et_2O yielded 238 mg (79.1%) of fluffy white **12**, mp 243–244 °C.

4-(3,4,5-Trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2). Method A. A solution containing 100 mg (0.18 mmol) of 4-(3,4,5-trimethoxybenzyl)-

6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (12) dissolved in 100 mL of anhydrous ethanol and 25 mg of 10% palladium-on-carbon catalyst was hydrogenated at 40 psi for 8 h. The solution was gravity filtered, concentrated in vacuo, and allowed to crystallize in a saturated Et_2O chamber. After recrystallization from methanol–Et_2O 53 mg (76.6%) of an off-white crystalline **2**, mp 264–265 °C, was obtained. Anal. ($C_{19}H_{24}O$-NCl·CH_3OH) C, 58.04; H, 6.82; N, 3.38. Found: C, 58.00; H, 6.46; N, 3.49. Mass spectrum (EI) *m/e* 345; mass spectrum (CI) *m/e* 346.

Method B. A solution containing 200 mg (0.36 mmol) of 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinoline hydrochloride (11) dissolved in 250 mL of anhydrous ethanol and 100 mg of 10% palladium-on-carbon catalyst was hydrogenated on a Parr apparatus at 25 °C for 16 h at an initial H_2 pressure of 48 psi. The solution was gravity filtered, concentrated in vacuo and filtered through a cotton plug. The solution was further concentrated in vacuo and filtered through a cotton plug. The solution was further concentrated to ca. 3 mL under a stream of argon and allowed to crystallize in a saturated Et_2O chamber. After recrystallization from methanol–Et_2O, 136 mg (83.6%) of off-white **2**, mp 264–265 °C, was obtained.

Biological Testing. Guinea pigs of either sex weighing 300–500 g were used in these experiments. The procedures for the pharmacological testing of each compound in isolated tracheal strip and right atrial preparations were identical with those previously described.[2a] In all biological experiments the ED_{50} values represent the concentration of each agonist required to produce a response equal to one-half of the maximal response in the appropriate system.

Drug solutions were prepared in normal saline containing 0.05% sodium metabisulfite.

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References and Notes

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Isoquinolines. 5.[1] Synthesis and Antiarrhythmic Activity of Benzylisoquinoline Derivatives[2]

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The synthesis of a series of benzylisoquinolines **2–9** containing aminoacetamide side chains is described. The method involved reduction of the appropriately substituted nitrobenzylisoquinolines followed by acylation to the chloroacylamide derivatives. Amination with the appropriate amine yielded the desired secondary and tertiary amines. The primary amines were prepared via the phthalimides. Two acetanilides **14** and **15** are also described and compared with the benzylisoquinoline derivatives. All compounds were evaluated for their ability to protect against chloroform-induced ventricular fibrillation in mice. The active compounds **6** and **7** were tested for their effect against ventricular arrhythmias in dogs with myocardial infarction. All compounds with the exception of **5** and **12** exhibited some antiarrhythmic effect. The most potent compound, 1-[2-(2-ethylaminoacetyl)amino-3,4-dimethoxybenzyl]isoquinoline (**7**), showed greater antiarrhythmic potency, was considerably less toxic than lidocaine, and is a candidate for further evaluation.

Presently, the most widely used antiarrhythmic drugs are quinidine, procainamide, diphenylhydantoin, lidocaine, and propranolol.[3] In order to improve the therapeutic ratio of such amide-type antiarrhythmic agents as procainamide and lidocaine, we wished to examine certain derivatives of papaverine (**1**), a drug which has been well recognized for its spasmolytic and coronary vasodilator activity and, to a lesser extent, for its antiarrhythmic effects.[4] The synthesis of a series of benzylisoquinolines **2–9**, structurally related to lidocaine, containing an amino group partially ionized at physiological pH, and an amide function, was thus undertaken. The tetrahydroisoquinoline **13** was also prepared and compared with (±)-laudanosine (**12**), a related isoquinoline lacking the amine and amide functional groups. Two additional compounds **14** and **15**, which can be considered as dissected analogues of **2** and **5**, lacking