Synthesis of 1-Substituted Analogues of Trimetoquinol Possessing Differential and Selective β-Adrenergic Properties

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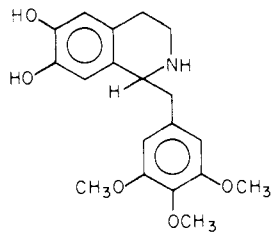
The synthesis of the 1,1-disubstituted tetrahydroisoquinoline analogues, 1-methyl-1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**2**) and 1-benzyl-1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**3**), is described. The profile of β-adrenergic activity for these analogues was determined and compared to that of trimetoquinol (**1**) in isolated guinea pig atrial, tracheal, and rat adipocyte preparations. Unexpected selective β_1-blocking activity in guinea pig trachea was noted with analogue **3**. With the exception of **2** in guinea pig atria, **2** and **3** did not possess any β-stimulant activity. Substitution at the 1 position of trimetoquinol (**1**) has revealed qualitative differences in β-adrenergic activity.

Trimetoquinol (**1**) is used clinically in Japan as a bronchial relaxant and is known to possess potent β_1- and β_2-stimulant properties.[1-3] We have previously examined the profile of β-adrenergic activity for a number of trimetoquinol analogues; the majority of these efforts were concerned with fragmented derivatives of trimetoquinol.[1-5] This report is concerned with the addition of functional groups to trimetoquinol (**1**) and the effect such groups have upon β-adrenergic activity. In a continuing effort to develop more selective adrenergic stimulants, the effect of the addition of a methyl and benzyl group to the 1 position of trimetoquinol to give **2** and **3**, respectively, was examined.



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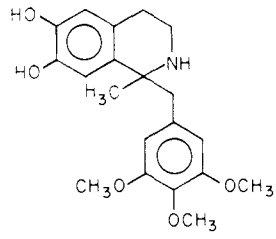

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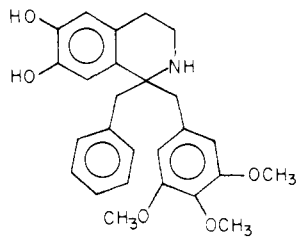

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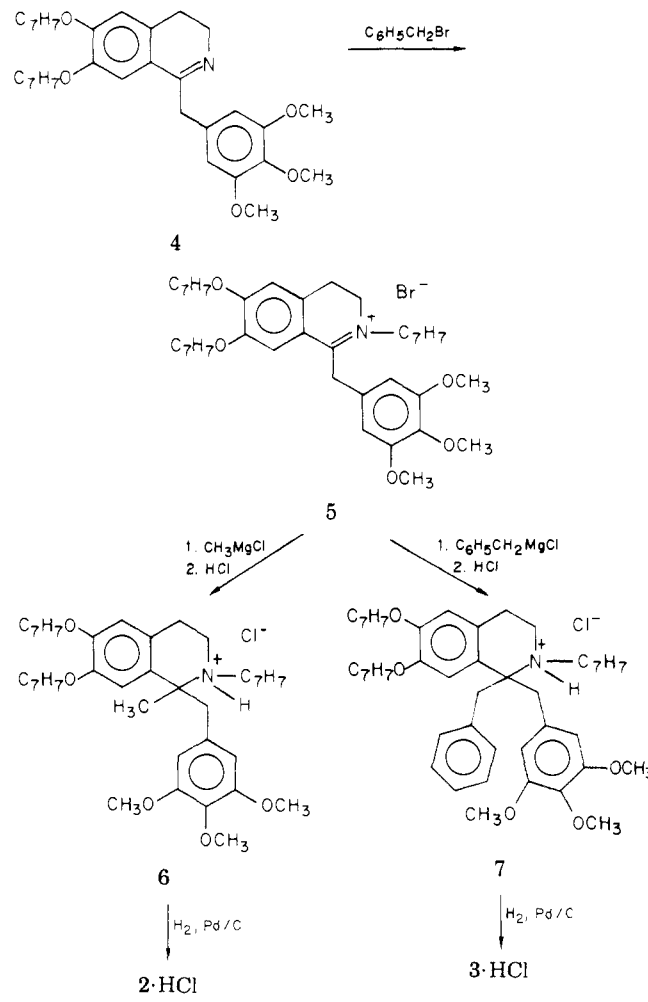
In considering trimetoquinol as a cyclized catecholamine, we were interested in what effect increasing the bulk at the 1 position of trimetoquinol would have upon β-adrenergic activity. More specifically we chose to examine the role of a smaller substituent, methyl, vs. a larger substituent, benzyl, on the relative affinities of these compounds for β_1- and β_2-adrenergic receptor systems.

Chemistry. The synthesis of compounds **2** and **3** began with the treatment of 1-(3,4,5-trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinoline (**4**)[1] with benzyl bromide to afford the quaternary salt **5** (Scheme I). It has been shown by several investigators[6-11] that quaternary salts of Schiff bases undergo reactions with Grignard reagents. When an Et_2O suspension of **5** was allowed to react with methylmagnesium iodide in Et_2O under refluxing conditions followed by work-up and hydrochloride salt formation, the desired 1,1-disubstituted tetrahydroisoquinoline **6** was isolated. The benzyl groups were removed from **6** by catalytic hydrogenation over 10% Pd/C

Scheme I



to afford the desired catechol **2**. In the preparation of **3** the first attempts at treating a THF suspension of the quaternary salt **5** with excess benzylmagnesium chloride under refluxing conditions resulted in the isolation of an extensive amount of polymeric material and small amounts of the desired product. However, it was established that when the salt of **5** was added to a large excess of the Grignard reagent at room temperature, the mixture would turn clear and a normal work-up followed by hydrochloride salt formation gave good yields of the desired product **7**. Catalytic hydrogenation using 10% Pd/C allowed for removal of the benzyl-protecting groups and afforded the desired catecholamine **3**.

Biological Results and Discussion. The pharmacological interaction of compounds **2** (1-Me-TMQ), **3** (1-

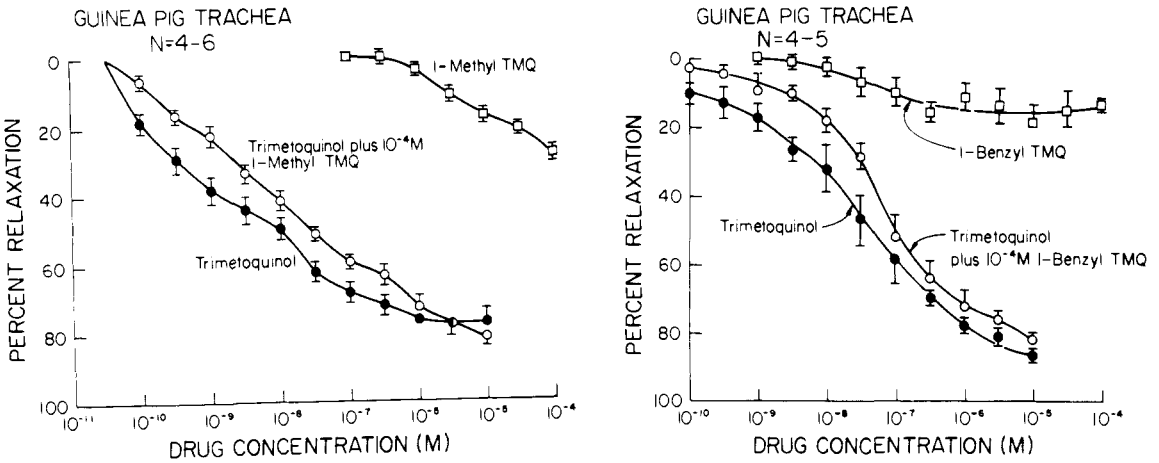


Figure 1. Dose–response curves for the interaction of trimetoquinol (1), 1-Me-TMQ (2), and 1-Bzl-TMQ (3) in isolated guinea pig tracheal strip preparations. Left frame: (●–●) 1 alone; (○–○) 1 in the presence of 10^{-4} M 1-Me-TMQ (2); and (□–□) 2 alone. Right frame: (●–●) 1 alone; (○–○) 1 in the presence of 10^{-4} M 1-Bzl-TMQ (3); and (□–□) 3 alone. Values represent the mean ± SEM of N = 4–6.

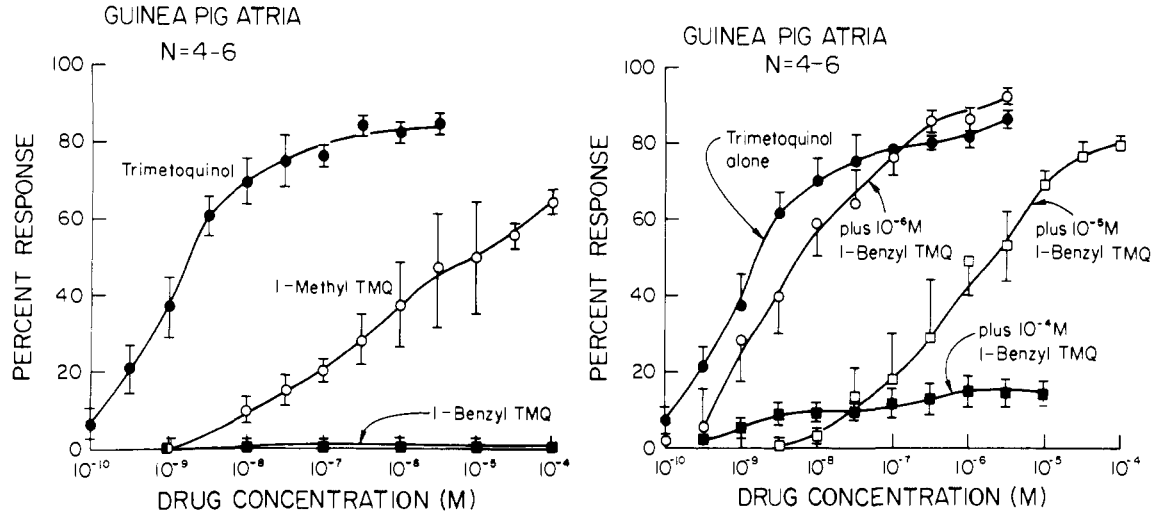


Figure 2. Dose–response relationships for the interaction of trimetoquinol (1), 1-Me-TMQ (2), and 1-Bzl-TMQ (3) in isolated guinea pig right atria preparations. Left frame: (●–●) 1 alone; (○–○) 2 alone; (■–■) 3 alone. Right frame: dose–response curve for 1 alone (●–●) or in the presence of 10^{-6} M 3 (○–○), 10^{-5} M 3 (□–□), and 10^{-4} M 3 (■–■). Values represent the mean ± SEM of N = 4–6.

Bzl-TMQ), and trimetoquinol (TMQ, 1) with guinea pig tracheal and atrial preparations is given in Figures 1 and 2, respectively. Both compounds 2 and 3 were unable to produce significant tracheal relaxation or lipolysis in the dose range 10^{-9}–10^{-4} M, while trimetoquinol was observed to be a potent β-stimulant in these preparations (pD_2 = 7.0) in both adrenergic systems. Neither 2 nor 3, at 10^{-4} M, was observed to block trimetoquinol-induced relaxation of guinea pig trachea (see Figure 1).

Only the 1-methyl analogue 2 possessed weak agonist activity in the guinea pig atrial preparation (Figure 2). Of interest, however, is the observation that the 1-benzyl analogue 3 was an antagonist of the chronotropic response to trimetoquinol in the guinea pig atrial preparation as shown in Figure 2. In a series of time–response studies using 10^{-4} M 3, it was observed that this compound reduced the basal atrial rate; the maximum negative chronotropic response to 3 was not overcome by addition of high concentrations (10^{-3} M) of isoproterenol or trimetoquinol. Atrial rates in the presence of 10^{-4} M 3 were decreased to less than 10% of the basal level within 45 min. Under the same experimental conditions, no negative chronotropic response was noted with 10^{-5} or 10^{-6} M 3. In Figure 2, a competitive inhibition of TMQ-induced chronotropic response was observed in the presence of 10^{-6} and 10^{-5} M 3, as indicated by the parallel shifts in the dose–response curves. As can also be noted, the chronotropic response in the presence of 10^{-4} M 3 was not overcome by the addition of trimetoquinol. Nevertheless, from the results obtained for 3 in guinea pig atria and trachea, this analogue appears to be a selective β-antagonist. By contrast, trimetoquinol is a potent β-adrenergic stimulant in these isolated preparations, as has been reported previously.[1-3] Clearly, disubstitution at the 1 position of trimetoquinol has altered the β-adrenergic activity exhibited by analogues 2 and 3. It is also of interest to note that analogue 2 produced qualitatively different actions in guinea pig atria (partial agonist) and rat adipose tissue although these systems are classified as β_1-adrenergic receptor systems.[12]

In our investigations of a variety of modifications of the structure of trimetoquinol (1),[1-5] only the addition of a benzyl group to trimetoquinol to give analogue 3 resulted in specific β-adrenergic blocking activity which was selective for chronotropic action in the heart. Moreover, few biological studies have appeared in the literature which have evaluated the β-adrenergic activity of 1,1-disubstituted tetrahydroisoquinolines. Gray et al.[13] reported that 1,1-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline possessed extremely weak stimulatory activity in rabbit atrium and antagonist activity was not reported. Based upon our findings, further investigations are warranted in

studying 1,1-disubstituted tetrahydroisoquinolines for their activity in adrenergic systems.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Perkin-Elmer 257 infrared spectrophotometer, a Beckman 4230 infrared spectrophotometer, a Varian A-60A nuclear magnetic resonance spectrometer at 60 MHz or a Bruker HX 90E nuclear magnetic resonance spectrometer at 90 MHz, and a Dupont 491 mass spectrometer (EI mass spectra were obtained at 70 eV via direct probe). Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical results for elements indicated were within ±0.4% of the theoretical values.

2-Benzyl-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinolinium Bromide (5). Benzyl bromide (1.2 mL, 0.01 mol) was added in one portion to a solution of **4** (2.0 g, 0.0042 mol) in dry benzene. The mixture was refluxed for 3.5 h under nitrogen during which time the salt precipitated. The mixture was cooled to room temperature and filtered, and the precipitate was washed with benzene followed by Et_2O. The salt was recrystallized from dry 2-propanol to give 2.5 g (86%) of **5**: mp 199–202 °C. Anal. ($C_{40}H_{40}NO_5Br$) C, H, N.

1-Methyl-1-(3′,4′,5′-trimethoxybenzyl)-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6). To a Grignard solution prepared from 0.83 g (0.035 mol) of Mg turnings and 4.9 g (0.035 mol) of MeI in 50 mL of dry Et_2O, 1.22 g (0.0018 mol) of **5** was added as a suspension in dry Et_2O (40 mL) over 10 min, and the mixture was refluxed with stirring for 24 h. The cooled reaction mixture was poured onto crushed ice containing 3 g of NH_4Cl in 40 mL of H_2O. The mixture was basified with 10% NH_4OH aqueous solution and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give 0.71 g of the free base. The HCl salt was formed and recrystallized from Et_2O–MeOH: mp 108–110 °C. Anal. ($C_{41}H_{44}NO_5Cl$) C, H, N.

1-Methyl-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2). To a solution of **6** (0.8 g, 0.0012 mol) in 70 mL of absolute EtOH, 10% Pd/C (325 mg) was added. The mixture was hydrogenated at room temperature at 40 psi on a Parr apparatus for 8 h and then filtered with the aid of Celite. The solvent volume was reduced to 4 mL under reduced pressure and Et_2O (2.0 mL) was added. The solid which deposited on standing was collected by filtration to give **2** (0.42 g, 88%): mp 173–175 °C; mass spectra electron-impact molecular ion (M^+) at m/e 359. Anal. ($C_{20}H_{26}NO_5Cl \cdot H_2O$) C, H, N.

1-Benzyl-1-(3′,4′,5′-trimethoxybenzyl)-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (7). To a stirred mixture of 18 mL (0.036 mol) of commerical benzylmagnesium chloride (Aldrich, 1.97 M in THF) in 50 mL of dry THF under nitrogen was added dropwise, at room temperature, a suspension of 1.22 g (0.0018 mol) of **5**. The mixture was stirred until it turned clear (5–10 min) and then poured into a solution of 4 g of NH_4Cl in 50 mL of ice–water. The mixture was extracted with $CHCl_3$ and the organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give a clear oil. The oil was purified by silica gel column chromatography (benzene–ether, 9:1) to give 1.1 g (88%) of a clear oil. The HCl salt **7** was prepared and collected as a white solid: mp 209–212 °C. Anal. ($C_{47}H_{47}NO_5$) C, H, N.

1-Benzyl-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3). To a solution of the HCl salt of **2** (0.6 g, 0.008 mol) in 60 mL of absolute MeOH, 300 mg of 10% Pd/C was added. The mixture was hydrogenated on a Parr apparatus at room temperature at 40 psi for 8 h. The mixture was filtered with the aid of Celite, and the solvent was reduced to ~3 mL under reduced pressure. Et_2O (2 mL) was added to the solution. The solid which deposited on standing was collected by filtration to give 0.36 g (76%) of **3**: mp 163–165 °C. Anal. ($C_{26}H_{30}NO_5Cl$) C, H, N.

Biological Testing. Guinea pigs of either sex (weighing 300–500 g) and male Sprague–Dawley rats (weighing 180–250 g) were used in these experiments. The procedures for the pharmacological testing of each compound in isolated fat adipocyte, tracheal strip, and right atrial preparations were identical with those methods described previously.[4] Our studies did not include the use of an α-adrenergic blocking agent or COMT inhibitor. In experiments designed to evaluate antagonist properties, drugs were preincubated with guinea pig atrial and tracheal preparation for 30 min before the addition of trimetoquinol. Dose–response curves for trimetoquinol were completed within 1 h after the preincubation period. Drug solutions were prepared in normal saline containing 0.05% sodium metabisulfite.

References and Notes

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Isoquinolines. 6. Potential Central Nervous System Antitumor Agents.[1] Nitrogen Mustards of 3-Amino-4-(*p*-aminophenyl)isoquinoline

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A series of 3-amino-4-(*p*-aminophenyl)isoquinolines bearing the bis(2-chloroethyl)amino group was synthesized as potential CNS antitumor agents. Diol precursors **1e** and **1f** were prepared by the treatment of **1b** and **1c** with ethylene oxide. Diol precursors **5a–c** and **9** were prepared by the treatment of **4a–c** and **8** with diethanolamine. The reaction of these diols with $SOCl_2$ yielded target mustards **10–15** which were evaluated in the intraperitoneal murine L1210 tumor. No intermediates or target mustards were active in this tumor system.

In a recent review of central nervous systems (CNS) antitumor agents,[2] Broder and Rall concluded that the emphasis for new drug design should be placed on alkylating agents that can penetrate the blood–brain barrier