the same temperature, the organic phase was separated, washed with H_2O, filtered, and evaporated at reduced pressure to afford a solid residue (0.18 g), which was crystallized from benzene/petroleum ether (bp 30–60 °C) to yield pure cyclic carbamate **8** (0.09 g, 42%): mp 173–174 °C; IR (Nujol) ν 1735 cm^{-1} (C=O). Anal. ($C_{28}H_{27}NO_4$) C, H, N.

***endo*-3-Amino-*exo*-2-(3,4-dihydroxyphenyl)-2-hydroxybicyclo[2.2.1]heptane Hydrochloride (4a·HCl).** A solution of **7** (0.50 g, 1.2 mmol) in 1:1 CH_2Cl_2/anhydrous EtOH (20 mL) was stirred under hydrogen at 50 °C and atmospheric pressure in the presence of 10% palladium on charcoal (0.20 g). When the absorption stopped, the catalyst was filtered off and the solution was acidified to pH 5 with Et_2O·HCl. Evaporation of the solution gave a solid residue, which was crystallized from MeOH/Et_2O to yield pure **4a**·HCl (0.18 g, 55%): mp 199–201 °C dec; ^1H NMR δ 1.13–2.18 (br, 6 H), 2.38–2.76 (br, 2 H), 3.39 (d, 1 H, J = 4.5 Hz, C*H*N), and 6.63–7.18 (m, 3 H). Anal. ($C_{13}H_{18}ClNO_3$) C, H, N.

***exo*-2-(3,4-Dihydroxyphenyl)-2-hydroxy-*endo*-3-(isopropylamino)bicyclo[2.2.1]heptane Hydrochloride (4b·HCl).** A solution of **7** (0.40 g, 0.96 mmol) was dissolved in anhydrous MeOH (2 mL) and treated for 14 h with Me_2CO (2 mL). The solution was then shaken under hydrogen at 50 °C and atmospheric pressure in the presence of 10% palladium on charcoal (0.20 g). After 7 h at the same temperature, the catalyst was removed by filtration and the resulting solution was made slightly acid (ca. pH 5.5) with Et_2O·HCl. Evaporation of the solution yielded a semisolid residue, which was crystallized from MeOH/Et_2O to give pure **4b**·HCl (0.040 g, 32%): mp 158–160 °C dec; ^1H NMR δ 1.26 (2 d, 6 H, J = 6.6 Hz, CH*Me*$_2$), 1.40–2.12 (br, 6 H), 2.43–2.73 (br, 2 H), 2.54 (m, 1 H, J = 6.6 Hz, C*H*Me$_2$), 3.60 (d, 1 H, J = 4.4 Hz, C*H*NHCHMe$_2$), and 6.74–7.15 (m, 3 H). Anal. ($C_{16}H_{24}ClNO_3$) C, H, N.

Pharmacological Methods. Isolated Rat Vas Deferens. α-Adrenoceptor activity was evaluated on isolated vasa deferentia obtained from reserpinized adult albino Sprague–Dawley rats as previously described.[18]

Isolated Guinea Pig Atria and Tracheal Strips. The tests for β_1- and β_2-adrenoceptor activity were performed, in accordance to ref 2, on isolated preparations obtained from male adult guinea pigs (weight range 300–350 g).

The following drugs were used as salts: **1a** (*l*-norepinephrine) as bitartrate, **1b** (*l*-isoproterenol), carbachol, phentolamine, and the cyclic compounds **4a** and **4b**, as hydrochlorides. Reserpine was used as a free base solution (Serpasil).

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Registry No. **4a**, 118891-94-4; **4a**·HCl, 118891-92-2; **4b**, 118891-95-5; **4b**·HCl, 118891-93-3; **5**, 28043-14-3; **6**, 118891-89-7; **7**, 118920-11-9; **7**·HCl, 118891-90-0; **8**, 118891-91-1; [3,4-bis(benzyloxy)phenyl]magnesium bromide, 16047-57-7.

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Design and Synthesis of Propranolol Analogues as Serotonergic Agents

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Serotonin (5-HT) binds with nearly identical affinity at the various central 5-HT binding sites. Few agents bind with selectivity for 5-HT_{1A} sites. The β-adrenergic antagonist propranolol binds stereoselectively both at 5-HT_{1A} and 5-HT_{1B} sites (with a several-fold selectivity for the latter) and, whereas it is a 5-HT_{1A} antagonist, it appears to be a 5-HT_{1B} agonist. As such, it could serve as a lead compound for the development of new 5-HT_{1A} and 5-HT_{1B} agents. The purpose of the present study was to modify the structure of propranolol in such a manner so as to reduce its affinity for 5-HT_{1B} and β-adrenergic sites while, at the same time, retaining its affinity for 5-HT_{1A} sites. Removal of the side-chain hydroxyl group of propranolol, and conversion of its secondary amine to a tertiary amine, reduced affinity for 5-HT_{1B} and β-adrenergic sites. In addition, shortening the side chain by one carbon atom resulted in compounds with affinity for hippocampal 5-HT_{1A} sites comparable to that of racemic propranolol, but with a 30- to 500-fold lower affinity for 5-HT_{1B} sites and a greater than 1000-fold lower affinity for β-adrenergic sites. The results of these preliminary studies attest to the utility of this approach for the development of novel serotonergic agents.

The last several years have seen a growing interest in the neurotransmitter serotonin (5-HT); this is primarily due to the identification of several central 5-HT binding sites (i.e., 5-HT_1, 5-HT_2, 5-HT_3 sites) and the realization that these sites may be responsible for controlling various physiological functions of 5-HT. Of the various populations of central 5-HT binding sites, the 5-HT_{1A} sites have perhaps been the best studied and have generated the most interest.[1,2] It has been proposed that 5-HT_{1A} receptors may be involved in, for example, temperature regulation, sexual activity, appetite control, and, most recently, the mechanism of action of a new class of anxiolytic agents (i.e., second-generation arylpiperazine anxiolytics).[1-3]

The most useful and selective 5-HT_{1A} agonist is 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; **1**), and [^3H]8-OH-DPAT is now employed as a radioligand to label 5-HT_{1A} sites.[2] At one time, it was suspected that 5-HT_1 sites might represent "agonist" sites and that 5-HT_2 sites were "antagonist" sites [for discussion, see ref 1 and 3]. Currently, there is little support for this notion; nevertheless, there is still a lack of 5-HT_{1A}-selective antagonists. To date, the only agents consistently shown to behave as 5-HT_{1A} antagonists (other than a few nonselective

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Table I. Properties of the New (Aryloxy)alkylamines

$ArX(CH_2)_nNRR'$

	Ar	n	R	R'	mp,[a] °C	% yield	recyst solvent	formula[b]
7	2-OMePh	3	Me	Me	129–130	40	iPrOH/Et_2O	$C_{12}H_{19}NO_2$·HCl
11	Naph[c]	3	nPr	nPr	149–150	80	iPrOH	$C_{19}H_{27}NO$·HCl
13	Naph	4	Me	Me	160–161	40	EtOAc	$C_{16}H_{21}NO$·HCl
15	Naph	3	nBu	nBu	131–132	39	$CHCl_3/Et_2O$	$C_{21}H_{31}NO$·HCl
16	Naph	2	nBu	nBu	128–129	20	EtOAc	$C_{20}H_{29}NO$·HCl
17[d,e]	Naph	2	Me	nPr	153–154	95	iPrOH	$C_{16}H_{21}NO$·HCl
18[f]	Naph	2	Me	Bn[g]	192–194	80	iPrOH	$C_{20}H_{21}NO$·HCl
19	Naph	2	Et	nBu	110–111	33	EtOAc	$C_{18}H_{25}NO$·HCl

[a] Hydrochloride salt. [b] All compounds analyzed for C, H, N ±0.4% of theory. [c] Naph = 1-naphthyl. [d] Prepared by heating in a sealed tube. [e] bp (free base) 56–65 °C, 0.05 mmHg. [f] bp (free base) 70–85 °C, 1.0 mmHg. [g] Bn = benzyl.

5-HT antagonists that, if anything, appear to be selective for other populations of 5-HT sites) are certain β-adrenergic antagonists such as propranolol (**2**) and pindolol. These agents can antagonize, for example, (a) the hypothermic effects,[4] (b) the discriminative stimulus effects,[5] (c)the microiontophoretic effects,[6] and (d) the "serotonin syndrome"[7] produced by various 5-HT_{1A} agonists including 8-OH-DPAT. This antagonism seems to be mediated via a serotonergic mechanism and there is no evidence of adrenergic involvement. Indeed, propranolol and pindolol bind in a stereoselective manner to 5-HT_{1A} sites.[8-10] Obviously, these adrenergic agents are not selective for 5-HT sites because they possess an even greater affinity for β-adrenergic sites. Furthermore, these agents bind at 5-HT_{1A} and at 5-HT_{1B} sites with nearly comparable affinity,[10] and there is recent evidence suggesting that propranolol and/or pindolol can behave as 5-HT, and in particular as 5-HT_{1B}, agonists.[11-13] Nevertheless, these agents represent one of the few structural leads that might be exploited for the development of 5-HT_{1A}-selective antagonists and 5-HT_{1B}-selective agents. The purpose of the present investigation was to modify the structure of propranolol in such a manner as to abolish or decrease its affinity for 5-HT_{1B} and β-adrenergic receptors while, at the same time, retaining its affinity for 5-HT_{1A} sites. The general strategy was to eliminate those structural aspects of propranolol that are known to be important for adrenergic action and to take advantage of our observation[1,14] that tertiary amines generally display a reduced affinity for 5-HT_{1B} sites relative to 5-HT_{1A} sites.

Chemistry

Compound **7** was prepared by allowing 2-methoxyphenol to react with 1,3-dibromopropane, followed by reaction of the phenoxypropyl bromide with dimethylamine. Compounds **11**, **13**, and **15–19** (Table I) were prepared in a similar manner by using the appropriate (1-naphthyloxy)alkyl bromide[15,16] and amine. Compound **20** was prepared by reaction of 1-bromo-2-(1-naphthyloxy)ethane with potassium phthalimide and subsequent hydrolysis of the resulting phthalimide. Mannich reaction of 1-acetylnaphthalene with *N*-ethyl-*N*-*n*-butylamine afforded **22**. Catalytic reduction of **22** in ethanolic HCl afforded the methylene derivative **23**, whereas with $HClO_4$ in acetic acid, the tetrahydro derivative **24** was obtained. Compounds **4**,[17] **5**,[18] **6**,[19] **9**,[20] **10**,[21] **12**,[22] **14**,[21] and **21**[23] have been previously reported.

Results and Discussion

Features that are important for adrenergic activity include (a) an extended π (aromatic) system, (b) a four-atom chain separating the aromatic system from a terminal amine, (c) a terminal amine that is a secondary amine, (d) amine substituents that are bulky or branched, and (e) a hydroxyl group on the side chain.[24] Propranolol is also optically active and stereochemistry is important with regard to adrenergic activity. With use of a structurally simpler phenyl group, the first series of studies examined the importance of the phenolic oxygen atom for 5-HT_{1A} binding. Compounds **3–5** differ only with respect to the atom attached to the aromatic ring; although none of these compounds displayed high affinity for 5-HT_{1A} sites, it appears that the methylene analogue **3** offers no advantage over the oxygen analogue **5** and that the nitrogen analogue is essentially inactive (Table II). Unlike propranolol, however, compounds **3** and **5** already display modest selectivity for 5-HT_{1A} sites relative to 5-HT_{1B} sites. This is most likely the result of the tertiary amine (which is known to be detrimental at 5-HT_{1B} sites[14]); to confirm this possibility, the secondary amine derivative **6** was evaluated and found to be nonselective. Incorporation of a 2-methoxy or 2-hydroxy group has essentially no effect on affinity (i.e., **7** and **8**) whereas replacement of the dimethylamino

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Table II. Affinities of (Aryloxy)alkylamines and Related Agents for 5-HT_{1A} and Other Binding Sites

$ArX(CH_2)_nNRR'$

	X	Ar[b]	n	R	R'	K_i values,[a] nM 5-HT1A	5-HT1B	β-adrenergic
3	CH_2	Ph	3	Me	Me	5000 (750)	>10000	
4	NH	Ph	3	Me	Me	>25000	>10000	
5	O	Ph	3	Me	Me	4850 (500)	>10000	
6	O	Ph	3	Me	H	3300 (125)	3100 (250)	
7	O	2-OMePh	3	Me	Me	3000 (350)	>10000	
8	O	2-OH Ph	3	Me	Me	4900 (400)	>10000	
9	O	Ph	3	nPr	nPr	2750 (250)	>10000	
10	O	Naph	3	Me	Me	345 (20)	1000 (80)	2400 (235)
11	O	Naph	3	nPr	nPr	450 (20)	6100 (450)	
12	O	Naph	3[c]	nPr	nPr	1325 (200)	8000 (700)	
13	O	Naph	4	Me	Me	400 (25)	1000 (125)	
14	O	Naph	2	Me	Me	80 (5)	1500 (200)	4500 (950)
15	O	Naph	3	nBu	nBu	225 (25)	5650 (550)	8300 (850)
16	O	Naph	2	nBu	nBu	150 (20)	9000 (900)	>10000
17	O	Naph	2	Me	nPr	45 (10)	1800 (70)	5300 (980)
18	O	Naph	2	Me	Bn	95 (5)		
19	O	Naph	2	Et	nBu	39 (2)	1100 (80)	5000 (300)
20	O	Naph	2	H	H	60 (5)		
21		Naph	1	Me	Me	3420 (200)		
22	C=O	Naph	2	Et	nBu	3530 (390)		
23	CH_2	Naph	2	Et	nBu	300 (35)		
24	CH_2	Naph[d]	2	Et	nBu	540 (55)		
(±)-propanolol (**2**)						90 (15)	50 (15)	2.4 (0.1)
(−)-propanolol						55 (5)	17 (4)	
(+)-propanolol						1700 (120)		

[a] K_i values followed by SEM. In all cases, Hill slopes were 0.8–1.2, except for compound **12** at 5-HT_{1A} sites (0.70), and (±)-propranolol at β-adrenergic sites (0.74); Hill slopes were not determined where K_i > 10000 nM. [b] Ph = phenyl; Naph = 1-naphthyl. [c] Hydroxylated chain, i.e., $-CH_2CH(OH)CH_2-$. [d] 1,2,3,4-Tetrahydronaphthyl.

groups of **5** with a di-*n*-propylamino group (i.e., **9**) appears to double affinity.

The naphthyloxy derivatives **10** and **11** display a 10-fold greater affinity for 5-HT_{1A} sites than do their phenoxy counterparts **5** and **9**, respectively; however, there is a concomitant increase in affinity at 5-HT_{1B} sites. The chiral carbon atom and hydroxyl group of propranolol are important for adrenergic activity.[24] The corresponding hydroxyl analogue of **11** (i.e., **12**) was prepared and tested as its racemate; interestingly, the hydroxyl group does not seem to be important for 5-HT_{1A} binding (Table II). In fact, the hydroxyl derivative **12** (K_i = 1325 nM) possesses only one-third the affinity of the nonhydroxylated compound **11** (K_i = 450 nM).

Up to this point, the compound with the highest affinity for 5-HT_{1A} sites is the dimethylamino derivative **10**. Because the three-carbon chain that separates the naphthyloxy group from the terminal amine of propranolol is believed to be an important feature for adrenergic activity,[24] we wished to examine examples of a two- and four-carbon chain. The four-carbon chain analogue **13** was essentially equipotent with **10** at 5-HT_{1A} and 5HT_{1B} sites. However, the two-carbon chain analogue **14** displays a 4-fold increase in affinity for 5-HT_{1A} sites with no increase in affinity, compared with **10**, for 5-HT_{1B} sites. As might have been anticipated, on the basis of the structural requirements for adrenergic binding, compound **14** displays a low affinity for β-adrenergic sites (Table II).

Examination of **15** and **16** reveals that introduction of the di-*n*-butylamino group results in a decreased affinity for 5-HT_{1B} and β-adrenergic sites but has little effect on affinity at 5-HT_{1A} sites. Compound **16** also displays about a 100-fold selectivity for 5-HT_{1A} sites relative to 5-HT_{1B} and β-adrenergic sites. Compounds such as **17** and **19** seem to offer a compromise; whereas they possess a reasonable affinity for 5-HT_{1A} sites (k_i = 45 and 39 nM, respectively) and greater than a 100-fold selectivity for 5-HT_{1A} sites relative to β-adrenergic sites, their selectivity for 5-HT_{1A} sites versus 5-HT_{1B} sites is only 30- to 40-fold. Nevertheless, both **17** and **19** possess a higher affinity/selectivity for 5-HT_{1A} sites than does propranolol. Other modifications of the terminal amine (e.g. **18–20**) and of the side chain (e.g. **21**, **22**) did not significantly enhance the affinity of these agents for 5-HT_{1A} sites. Compound **23**, the methylene analogue of **19**, and its 1,2,3,4-tetrahydro derivative **24**, display only about one-tenth the affinity of **19**.

Propranolol binds in a stereoselective manner at 5-HT_{1A}, 5-HT_{1B}, and β-adrenergic receptors. Indeed, a significant structural similarity has been recently reported for 5-HT and adrenergic receptors.[30] The goal of our work was to modify the structure of propranolol so as to achieve 5-HT_{1A} selectivity. Thus, we used the structure of this agent as a template for the synthesis of several novel agents. By removing the side-chain hydroxyl group, and by shortening the side chain from three to two carbon atoms, we significantly reduced the affinity of propranolol for β-adrenergic sites. Taking advantage of the fact that tertiary amines are not well tolerated by either 5-HT_{1B} or β-adrenergic sites, we ultimately obtained agents that display a relatively low affinity for these sites, yet retain affinity for 5-HT_{1A} sites. The present results validate the utility of this approach, and continued studies may result in newer agents with even greater affinity and selectivity for 5-HT_{1A} receptors. Using a similar strategy, it should also be possible to prepare agents that are selective for 5HT_{1B} sites.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalysis was performed by Atlantic Microlab Inc. (Atlanta, GA) and determined values are within 0.4% of theoretical. Proton NMR spectra were recorded on a JOEL FX90Q spectrometer, operating at 90 MHz, in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra were recorded on a Nicolet 5ZDX FT-IR spectrophotometer. All spectral data are consistent with the assigned structures.

N,N-Dimethyl-4-phenylbutylamine Hydrochloride (3). 1-Bromo-4-phenylbutane[25] (0.95 g, 4.5 mmol), dimethylamine hydrochloride (1.82 g, 22.5 mmol), and K_2CO_3 (3.12 g, 22.5 mmol) were heated at reflux in toluene for 24 h. The reaction mixture was allowed to cool; a saturated solution of Na_2CO_3 (15 mL) was added, the organic layer was removed, and the aqueous portion was extracted with toluene (2 × 25 mL). The toluene was removed in vacuo and an ethereal solution of the resulting oil was treated with Et_2O that had been previously saturated with HCl gas. The precipitate was collected by filtration and recrystallized from EtOAc to give 0.57 g (60%) of **3** as colorless needles: mp 130–131 °C. Anal. ($C_{12}H_{19}N\cdot HCl\cdot {}^1/_4H_2O$) C, H, N.

N,N-Dimethyl-3-(2-methoxyphenoxy)propanamine Hydrochloride (7). 1-Bromo-3-(2-methoxyphenoxy)propanamine[26] (1.0 g, 4.0 mmol) was added to a stirred mixture of K_2CO_3 (2.76 g, 20.0 mmol) and dimethylamine hydrochloride (1.66 g, 20.0 mmol) in warm toluene (100 mL). The reaction mixture was heated under reflux for 24 h. The solution was cooled to room temperature and the solvent was removed in vacuo. Saturated aqueous Na_2CO_3 (50 mL) was added to the residue and the solution was extracted with Et_2O (3 × 50 mL). The combined Et_2O portions were dried ($MgSO_4$) and evaporated under reduced pressure to yield 0.75 g of crude free base as a tan oil. A solution of the oil in 1 N HCl (25 mL) was washed with Et_2O (50 mL). The aqueous solution was made basic with a saturated aqueous solution of Na_2CO_3 (to pH 10) and extracted with Et_2O (3 × 50 mL), and the combined Et_2O fractions were dried ($MgSO_4$) and evaporated in vacuo. An Et_2O solution of HCl gas was added to a solution of the oil in anhydrous Et_2O until salt formation ceased. The salt was collected by filtration and recrystallized from 2-propanol/anhydrous Et_2O to give 0.4 g (40%) of **7** as colorless plates: mp 129–130 °C. Anal. ($C_{12}H_{19}NO_2\cdot HCl$) C, H, N.

Compounds **11**, **13**, and **15–19** were prepared in a manner comparable to that used for the preparation of **7**. The appropriate 1-naphthoxyalkyl bromide[26] was allowed to react with the desired amine to provide the products shown in Table I.

N,N-Dimethyl-3-(2-hydroxyphenyl)propanamine Hydrochloride (8). Compound **8**, as the free base, was prepared according to the general method of Krapcho.[26] A saturated solution of HCl gas in anhydrous Et_2O was added to an Et_2O solution of this oil until salt formation ceased. The salt was collected by filtration and recrystallized from 2-propanol to yield 0.1 g of **8** as a white solid: mp 149–150 °C. Anal. ($C_{11}H_{17}NO_2\cdot HCl$) C, H, N.

2-(1-Naphthyloxy)ethanamine Hydrochloride (20). 1-Bromo-(1-naphthyloxy)ethane (0.75 g, 2.99 mmol) and potassium phthalimide (0.66 g, 3.59 mmol) in DMF (5 mL) were heated on a steam bath for 3 h. After allowing the reaction mixture to cool, $CHCl_3$ (5 mL) was added, and the solution was poured into water (10 mL). The aqueous portion was extracted with $CHCl_3$ (2 × 15 mL) and the organic fractions were combined and washed with 1 N NaOH (2 × 5 mL). The $CHCl_3$ solution was dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting solid was recrystallized from CH_3CN to yield 0.62 g (65%) of *N*-(2-(1-naphthyloxy)ethyl)phthalimide: mp 130–132 °C. The hydrolysis of the phthalimide was performed by the general method of Ing and Manske;[27] the phthalimide (500 mg, 1.58 mmol) and hydrazine hydrate (85% solution 274 mg, (4.73 mmol of hydrazine)) were heated at reflux in absolute EtOH for 2 h. The hot reaction mixture was filtered and the filtrate was washed with EtOH; the EtOH fractions were combined and evaporated in vacuo. A basic solution (1 N NaOH, 5 mL) of the resulting oil was extracted with Et_2O (3 × 15 mL), and the combined organic fractions were dried ($MgSO_4$) and evaporated in vacuo. HCl in anhydrous Et_2O was added to an Et_2O solution of the product until salt formation ceased. The HCl salt was collected by filtration and recrystallized from 2-propanol to yield 0.2 g (64%) of a white solid: mp 252–255 °C. Anal. ($C_{12}H_{13}NO\cdot HCl$) C, H, N.

1-Amino-N-ethyl-N-n-butyl-3-(1-naphthyl)propan-3-one Hydrochloride (22). 1-Acetylnaphthalene (3.4 g, 20 mmol), *N*-ethyl-*n*-butylamine (2.8 g, 20 mmol), paraformaldehyde (0.8 g, 26 mmol) and concentrated HCl (0.5 mL) were combined in 2-propanol (4 mL) and heated at reflux for 6 h. The reaction was allowed to cool and EtOAc and Et_2O were added, and the reaction mixture was allowed to stand at −20 °C for 18 h. The precipitate was collected by filtration and recrystallized from EtOH/EtOAc (the compound is heat sensitive) to give 4.0 g (63%) of **22** as a white solid: mp 118–120 °C. Anal. ($C_{19}H_{25}NO\cdot HCl$) C, H, N.

N-Ethyl-N-n-butyl-3-(1-naphthyl)propanamine Hydrogen Oxalate (23). A solution of **22** (1.0 g, 3.3 mmol) and concentrated HCl (1 mL) in EtOH (60 mL) was shaken with 10% Pd/C (0.2 g) on a Parr hydrogenator at 45 psi for 8 h. The catalyst was removed by filtration and the solvent was removed by evaporation under reduced pressure. An aqueous KOH solution (pH 12) of the crude product was extracted with Et_2O (3 × 10 mL); the combined ethereal extracts were dried ($MgSO_4$) and evaporated to give an oil. The oil was added to a saturated solution of oxalic acid in absolute EtOH and the solid precipitate was collected by filtration. Recrystallization from EtOAc and then acetone afforded 0.3 g (25%) of the title compound as a white solid: mp 103–105 °C. Anal. ($C_{19}H_{27}N\cdot C_2H_2O_4$) C, H, N.

N-Ethyl-N-n-butyl-3-(1,2,3,4-tetrahydro-1-naphthyl)propanamine Hydrogen Oxalate (24). A solution of **22** (free base: 2.5 g, 8.2 mmol) and 70% $HClO_4$ (5 mL) in glacial HOAc (100 mL) was shaken with 10% Pd/C (0.4 g) on a Parr hydrogenator at 50 psi for 16 h. The crude product was isolated as with **23** except that the resulting oil was vacuum distilled (bp 116–120 °C/0.05 mmHg) prior to preparation of the salt. Recrystallization from acetone gave 1.1 g (35%) of **24** as a white solid: mp 118–120 °C. Anal. ($C_{19}H_{31}N\cdot C_2H_2O_4$) C, H, N.

Binding Studies. Tissue Preparation. Following decapitation, the brains of male Sprague-Dawley rats were removed, placed in 0.9% ice-cold saline, and dissected over ice until the tissue was prepared. Tissues were stored in ice-cold saline for not longer than 1 h and, following blot drying and weighing, were prepared and frozen at −30 °C until used. Freshly dissected (or frozen) tissue was homogenized (Polytron setting 6 for 20 s) in 30 volumes of ice-cold buffer containing 50 mM Tris·HCl (pH 7.4 at 37 °C; pH 8.0 at 4 °C), 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$ and centrifuged at 30000*g* for 15 min. The supernatent was discarded; the pellet was resuspended and preincubated for 15 min at 37 °C. The homogenate membranes were washed twice by centrifugation and resuspension. The final assay buffer contained 10 μM pargyline and 0.1% ascorbate was added last to the incubation medium. Protein determinations were made by the method of Lowry et al.[28]

Radioligand Binding Assays. The 5-HT_{1A} receptor was labeled with 0.1 nM [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]OH-DPAT) (157 Ci/mmol; New England Nuclear) and 4 mg wet weight of rat hippocampal tissue. 8-OH-DPAT (1 μM) was used to determine nonspecific binding. The 5-HT_{1B} receptor was labeled with 2.0 nM [^{3}H]5-HT and 8 mg of rat striatal membrane homogenate. 5-HT (10^{-6} M) was used to define nonspecific binding, and 10^{-7} M 8-OH DPAT and mesulergine were included to block 5-HT_{1A} and 5-HT_{1C} receptors, respectively. β-Adrenergic receptors were labeled by using 1.0 nM [^{3}H]dihydroalprenolol and 10 mg of rat frontal cortex homogenate with an incubation time of 20 min at 37 °C. Propranolol (1 μM) was used to determine nonspecific binding. Eleven concentrations of nonradioactive competing drugs were made fresh daily in assay buffer, and assays were performed in (at least) triplicate. Following incubation with membranes and radioligand at 37 °C for 30 min, samples were rapidly filtered over glass fiber filters (Schleicher and Schuell) and were washed with 10 mL ice-cold 50 mM Tris·HCl buffer. Individual filters were inserted into vials and equilbrated with 5 mL of scintillation fluid (ScintiVerse, Fisher) for 6 h before counting at 50% efficiency in a Beckman 3801 counter. Results were analyzed by using an updated version of the program EBDA[29] in order to determine IC_{50}, K_i, and Hill values.

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Registry No. 2, 525-66-6; 3, 95685-31-7; 3 free base, 1202-55-7; 4, 118868-54-5; 5, 20904-18-1; 6, 118868-55-6; 7, 118868-56-7; 7 free base, 75384-45-1; 8, 118868-57-8; 8 free base, 28204-46-8; 9, 118868-58-9; 10, 26243-11-8; 11, 118868-59-0; 11 free base, 118868-73-8; (±)-12, 118868-60-3; 13, 118868-61-4; 13 free base, 87272-77-3; 14, 26243-10-7; 15, 118868-62-5; 15 free base, 118868-74-9; 16, 118868-63-6; 16 free base, 118868-75-0; 17, 118868-64-7; 17 free base, 118868-76-1; 18, 118868-65-8; 18 free base, 117263-75-9; 19, 118868-66-9; 19 free base, 118868-77-2; 20, 118868-67-0; 20 free base, 50882-68-3; 21, 63722-04-3; 22, 118868-68-1; 22 free base, 118890-25-8; 23, 118868-70-5; 23 free base, 118868-69-2; 24, 118890-24-7; 24 free base, 118868-78-3; 1-bromo-4-phenylbutane, 13633-25-5; dimethylamine hydrochloride, 506-59-2; 1-bromo-3-(2-methoxyphenoxy)propanamine, 118868-71-6; *N*-(2-(1-naphthyloxy)ethyl)phthalimide, 118868-72-7; 1-acetylnaphthalene, 941-98-0; 1-(3-bromopropoxy)naphthalene, 3351-50-6; 1-(4-bromobutoxy)naphthalene, 87723-21-5; 1-(2-bromoethoxy)naphthalene, 13247-79-5; *N*-propyl-1-propanamine, 142-84-7; *N*-butyl-1-butanamine, 111-92-2; *N*-methyl-1-propanamine, 627-35-0; *N*-methylbenzenemethanamine, 103-67-3; *N*-ethyl-1-butanamine, 13360-63-9.

Conformationally Restricted Analogues of the Muscarinic Agent *N*-Methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide

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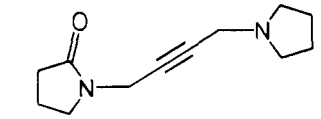
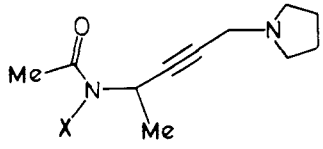
Conformationally restricted analogues of the selective partial muscarinic agonist *N*-methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide (BM 5; **2**) were synthesized. The compounds were tested for muscarinic and antimuscarinic activity in the isolated guinea pig ileum and in intact mice. They were found to be moderately potent muscarinic antagonists or weak partial agonists. The new compounds were less potent than **2** in inhibiting (−)-[^{3}H]-*N*-methylscopolamine binding in the rate cerebral cortex. Thus, structural modifications of **2** in which part of the amide moiety has been connected with the methyl group in the butynyl chain to form a five-membered ring decrease affinity and in most cases abolish efficacy.

A large series of oxotremorine (**1**)[1] analogues has been synthesized during the past 25 years.[2] Structural modifications of **1** include (a) reduction or prolongation of the intermediate butynyl chain, (b) introduction of substituents (mainly methyl groups) in the lactam ring, in the intermediate chain and in the pyrrolidine moiety, (c) variations of the amino moiety, including quaternization, (d) exchange of the pyrrolidone moiety for succinimide, phthalimide, and a large number of other ring systems, and (e) opening of the pyrrolidone ring. One of the more interesting derivatives is *N*-methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide (BM 5; **2**).[3] In contrast to **1**, which stimulates various muscarinic responses in a relatively uniform manner, **2** acts as an antagonist at some muscarinic sites (including certain presynaptic sites in the brain) while being an agonist at most others.[4,5] Thus, it has been suggested that **2** might have potential for the therapy of Alzheimer-type dementia and related disorders in which central cholinergic transmission is deficient.[6]



1



2 : X = Me

3 : X = MeCO

In the present paper we describe the synthesis and pharmacological evaluation of some conformationally restricted analogues of **2** in which, formally, the acetyl or the *N*-methyl substituent of the acetamide moiety has been connected with the methyl substituent in the butynyl chain. We have also included derivatives of the recently reported[7] acyclic imide **3** in this study.

The new compounds (**4**–**12**) were compared to **2** in their ability to inhibit the binding of the muscarinic antagonist (−)-[^{3}H]-*N*-methylscopolamine ([^{3}H]NMS) to homogenates of the rat cerebral cortex. They were also investigated for tremorogenic and tremorolytic activity in mice and for muscarinic and antimuscarinic activity on the isolated guinea pig ileum (Table II). None of the compounds had a pharmacological profile similar to that of **2**, which behaves like a partial agonist in the ileum and is a potent tremorolytic agent. However, **9** and **12** were partial agonists of weak potency and **7** and **10** were moderately potent tremorolytic agents.

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