Synthesis and Pharmacological Evaluation of Reduced Diastereoisomeric and Quaternary Ammonium Derivatives of Calcium Antagonistic (Methylenedioxy)indenes on the Isolated Rat Aorta[1]

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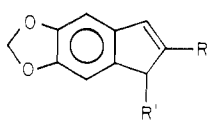
Based upon findings that 2-*n*-propyl- and 2-*n*-butyl-3-(dimethylamino)-5,6-(methylenedioxy)indenes (**1** and **2**) inhibit a variety of calcium-activated cellular processes, it has previously been proposed that these compounds act as calcium antagonists with an intracellular site of action. In the present investigation, the diastereoisomeric dihydro analogues, *cis*- and *trans*-2-*n*-propyl- and *cis*- and *trans*-2-*n*-butyl-1-(dimethylamino)-5,6-(methylenedioxy)indans (**5**–**8**), and the trimethyl quaternary ammonium analogues of the unsaturated (**3** and **4**) and cis-saturated (**9** and **10**) systems were synthesized, and the ability of each to reverse norepinephrine- or KCl-induced contraction of the rat aorta was assessed. Saturation of **1** or **2** to produce the corresponding *cis*-aminoindan analogues (**5** and **7**) yielded compounds of similar spasmolytic activity, while saturation which yielded the respective trans forms (**6** and **8**) resulted in significant loss of potency. Methylation of either the cis unsaturated or saturated compounds to yield their respective quaternary derivatives also significantly reduced the potency of each compound. The reduced activity of the quaternary derivatives might be anticipated because of the limited cellular penetration of such compounds and is taken as evidence that the active tertiary analogues have an intracellular site of action. However, the results of the present investigation do not preclude the contribution of membrane effects to the pharmacological activity of the tertiary compounds (**1**, **2**, **5**, and **7**), since the spasmolytically active analogues demonstrated a somewhat greater antagonistic potency against KCl-induced contractions as compared to their antagonism of the effects of norepinephrine.

Calcium antagonism—an antagonism of the influx of extracellular calcium and/or an interference with the mobilization, action, or availability of free intracellular calcium—is a property attributed to a wide spectrum of pharmacological agents with significant therapeutic value.[2-5]

A series of 2-substituted 3-(dimethylamino)-5,6-(methylenedioxy)indene hydrochlorides (MDIs) were synthesized in our laboratories,[6] and their pharmacological, biochemical, toxicological, electrophysiological, and structure–activity profiles have recently been reviewed.[2,3,7] An antagonism of the intracellular action and/or availability of calcium ions has been proposed to play a major role in the pharmacological mechanism of action of the two key MDIs **1** and **2**, which were extensively evaluated as



1, R = *n*-Pr; R′ = $N(CH_3)_2 \cdot HCl$
2, R = *n*-Bu; R′ = $N(CH_3)_2 \cdot HCl$
3, R = *n*-Bu; R′ = $N^+(CH_3)_3I^-$
4, R = *n*-Pr; R′ = $N^+(CH_3)_3I^-$

their HCl salts. Assignment of an intracellular calcium antagonistic mechanism of action to these two compounds is based upon their ability to interfere with barium-induced nonvascular (uterine and ileal) smooth-muscle contraction,[8] the reversibility of their vascular and nonvascular smooth-muscle relaxant properties by increasing extracellular calcium,[8,9] their ability to inhibit calcium-dependent (but not calcium-independent) evoked adrenomedullary catecholamine secretion without interfering with cellular calcium uptake,[10] their ability to reduce calcium release from the sarcoplasmic reticulum upon stimulation as evidenced by depression of activation heat in skeletal muscle,[11] their inhibitory effect on caffeine-induced contracture of skeletal muscle in the presence and in the absence of extracellular calcium,[12] their inhibitory effect on thrombin-induced platelet secretion,[13] their binding characteristics to cardiac troponin-C and to brain calmodulin with resultant inhibition of calcium calmodulin dependent processes,[14] and their inhibitory effect on swelling and uncoupling of oxidative phosphorylation induced by inorganic phosphates in isolated rabbit heart mitochondria.[15,16] The intracellular calcium antagonistic action of **1** and **2** probably contributes significantly to the pharmacological mechanism of action underlying their antiarrhythmic,[17-19] coronary dilating,[9] antihypertensive,[15]

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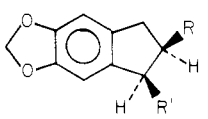
uterine relaxant,[8] intestinal antispasmodic,[8] and skeletal muscle relaxant properties.[12]

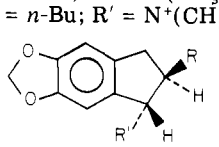
In an attempt to validate the intracellular nature of the calcium antagonistic action of **1** and **2**, a quaternary ammonium derivative (**3**) was synthesized. Such quaternary compounds do not readily gain access to the intracellular compartment. As expected, pharmacological experiments in vitro on the isolated, electrically driven guinea pig atria demonstrated the significantly weaker negative inotropic effect of **3** as compared to **1** and **2**.[9,20] Paradoxically, however, **3** was significantly more potent than tertiary amines **1** and **2** as an antiarrhythmic agent in vivo,[19] suggesting that **3** is metabolized in vivo to an active species.

Modifications resulting in decreased lipophilicity (2-Me or -Et) resulted in a reduction of calcium antagonistic potency,[8] whereas more lipophilic functions (2-*n*-heptyl, -cyclohexyl, and -phenyl) resulted in loss of calcium antagonistic activity and/or emergence of agonist activity.[21] Agonist activity observed for the 2-Ph analogue on the smooth muscle of the ileum was not blocked by atropine or a $PGF_{2\alpha}$ receptor blocker previously prepared in these laboratories,[22] but it was blocked by **2** and prenylamine, indicating an involvement of possibly both mobilization of intracellular calcium and increased calcium influx.[21] Replacement of the methylenedioxy group with dimethoxy substituents also resulted in a reduction of calcium antagonistic properties and emergence of agonist activity.[23]

In this study we assessed the comparative pharmacological profiles for the dihydro *n*-Pr (**5** and **6**) and *n*-Bu



5, R = *n*-Pr; R' = $N(CH_3)_2 \cdot HCl$
7, R = *n*-Bu; R' = $N(CH_3)_2 \cdot HCl$
9, R = *n*-Pr; R' = $N^+(CH_3)_3I^-$
10, R = *n*-Bu; R' = $N^+(CH_3)_3I^-$



6, R = *n*-Pr; R' = $N(CH_3)_2 \cdot HCl$
8, R = *n*-Bu; R' = $N(CH_3)_2 \cdot HCl$

(**7** and **8**) tertiary amine isomers and four quaternary compounds (**3**, **4**, **9**, and **10**). Pharmacological profiles for **3–10** were determined on the isolated aortic strip of the rat [contracted by norepinephrine (NE) or KCl] and compared to **1** and **2**. Inhibition of NE- and KCl-induced contractions of the isolated aorta is a characteristic property of calcium antagonists. Such compounds, in addition to being potentially valuable cardiovascular drugs,[2-5] could prove to be useful uterine muscle relaxants[8,24,25] for the management of premature labor. Uterine relaxant activity[24,25] has previously been predicted on the basis of relaxant properties on nonuterine smooth muscle.[22,26]

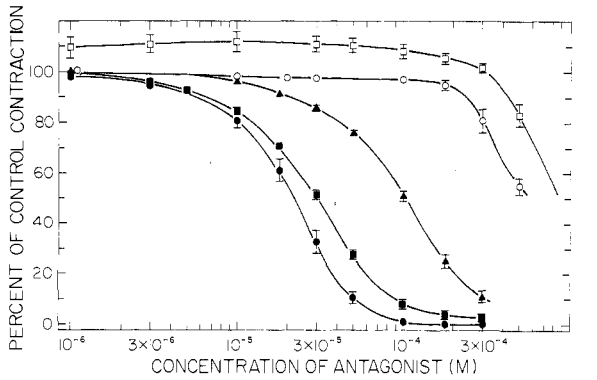


Figure 1. Cumulative effects of the propylaminoindenes and propylaminoindans on KCl-induced aortic contractions: (●) **1**, (■) **5**, (▲) **6**, (○) **4**, (□) **9**.

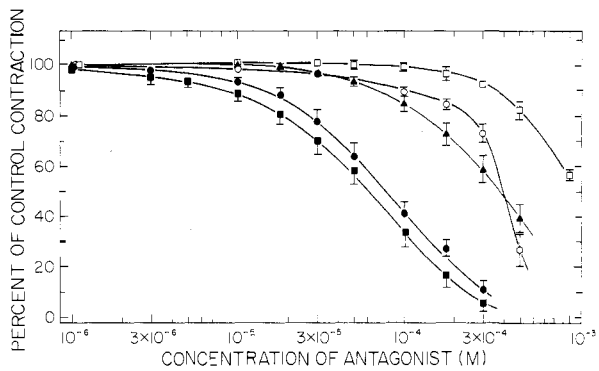


Figure 2. Cumulative effects of the propylaminoindenes and propylaminoindans on NE-induced aortic contractions: (●) **1**, (■) **5**, (▲) **6**, (○) **4**, (□) **9**.

Chemistry. Catalytic hydrogenation over platinum oxide of **1**·HCl and **2**·HCl afforded the expected diastereoisomeric mixtures of aminoindan hydrochlorides **5,6** and **7,8**, respectively, in 98% yield. The 8.5:1.5 ratio of cis to trans isomers formed is a reflection of catalytic reduction from the least hindered side of the molecule (i.e., the side opposite the dimethylamino group). Recrystallization of the diastereoisomeric mixtures from Et_2O/EtOH (20:1) afforded cis compounds free of trans isomers. Trans isomers (**6** and **8**) were isolated from their respective mother liquors by chromatography of the ether-soluble free bases on dry-packed silica gel employing EtOAc as the eluting solvent. Eluates, shown by TLC to contain the desired trans isomer, were combined and concentrated, and the residue was dissolved in Et_2O. Treatment with gaseous HCl afforded the minor isomer as a white precipitate.

Quaternary analogues **3**, **4**, **9**, and **10** were prepared in 50% yields from their corresponding tertiary amine free bases by reaction with excess MeI in absolute EtOH. Analogue purity was established by TLC and elemental and NMR analysis (see Experimental Section).

Pharmacological Results and Discussion

All observed effects with these compounds were reversible, since upon washout the tissues responded normally to NE and KCl. Relative potencies in relaxir g agonist-induced contraction of aortic strips, shown in Figures 1–4, were for the *n*-Pr compounds against NE-induced contractions: **1** = **5** > **6** = **4** > **9**; against KCl-induced contractions, **1** > **5** > **6** > **4** > **9**. For the *n*-Bu analogues against NE-induced contractions the relative potencies were **7** > **2** > **8** = **3** > **10**; against KCl-induced contractions

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Table I. IC_{50} Values for Aminoindans and Aminoindenes against NE- and KCl-Induced Aortic Contractions

test compd	IC_{50}, M (mean and range of SEM)		p^a
	norepinephrine (10^{-7} M)	potassium chloride (40 mM)	
1	7.82×10^{-5} (6.66×10^{-5} to 9.19×10^{-5})	2.14×10^{-5} (1.95×10^{-5} to 2.34×10^{-5})	<0.001
5	5.94×10^{-5} (4.94×10^{-5} to 7.10×10^{-5})	3.00×10^{-5} (2.89×10^{-5} to 3.11×10^{-5})	<0.002
6	3.83×10^{-4} (3.22×10^{-4} to 4.56×10^{-4})	9.89×10^{-5} (9.23×10^{-5} to 1.06×10^{-4})	<0.001
4	3.82×10^{-4} (3.40×10^{-4} to 4.20×10^{-4})	5.47×10^{-4} (5.13×10^{-4} to 5.84×10^{-4})	0.01
9	1.02×10^{-3} (9.10×10^{-4} to 1.15×10^{-3})	8.71×10^{-4} (6.98×10^{-4} to 1.09×10^{-3})	NS
2	7.41×10^{-5} (3.77×10^{-5} to 1.46×10^{-4})	2.03×10^{-5} (1.62×10^{-5} to 2.55×10^{-5})	<0.001
7	3.79×10^{-5} (3.22×10^{-5} to 4.43×10^{-5})	1.74×10^{-5} (1.58×10^{-5} to 1.91×10^{-5})	<0.001
8	1.51×10^{-4} (1.31×10^{-4} to 1.73×10^{-4})	3.11×10^{-5} (2.85×10^{-5} to 3.41×10^{-5})	<0.001
3	1.28×10^{-4} (1.02×10^{-4} to 1.61×10^{-4})	1.69×10^{-4} (1.54×10^{-4} to 1.85×10^{-4})	NS
10	2.81×10^{-4} (2.52×10^{-4} to 3.12×10^{-4})	1.75×10^{-4} (1.67×10^{-4} to 1.84×10^{-4})	<0.002

[a] Level of significance.

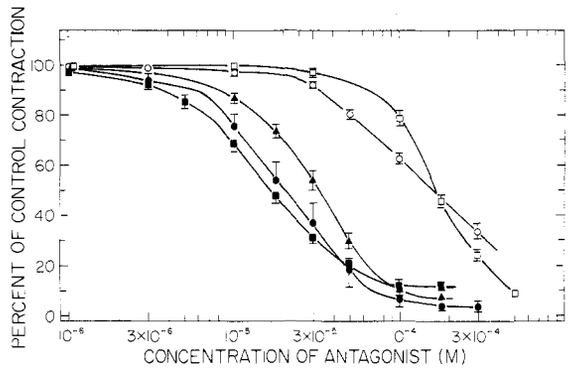

Figure 3. Cumulative effects of the butylaminoindenes and butylaminoindans on KCl-induced aortic contractions: (●) **2**, (■) **7**, (▲) **8**, (○) **3**, (□) **10**.

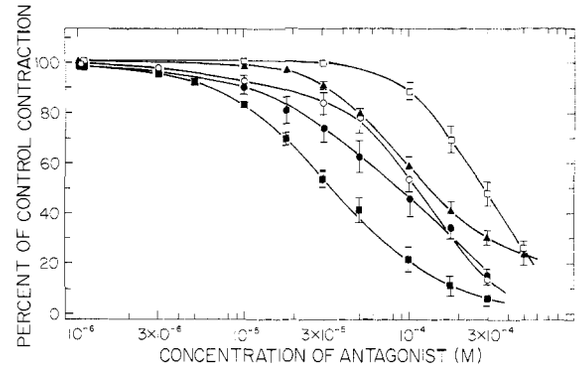

Figure 4. Cumulative effects of the butylaminoindenes and butylaminoindans on NE-induced aortic contractions: (●) **2**, (■) **7**, (▲) **8**, (○) **3**, (□) **10**.

they were **7 = 2 > 8 > 3 = 10**. Significance of differences was calculated at the 0.05 level using analysis of variance and Duncan's multiple range test. The similar relative order of decreasing potencies against both NE- and KCl-induced contractions for each series (*n*-Pr and *n*-Bu) provides convincing evidence that these compounds exert their effects through a common mechanism. Furthermore, the markedly decreased potencies of the quaternary derivatives provides evidence for an intracellular site of action. Specifically, aminoindan quaternary compounds (**9** and **10**) were always less potent than any tertiary amines, and the aminoindene quaternary compounds (**3** and **4**) were always less potent than the tertiary aminoindenes **1** and **2** or *cis*-aminoindans **5** and **7**.

Stereoselectivity also was observed. The *trans*-aminoindans **6** and **8** were always less potent than their respective *cis*-aminoindan isomers **5** and **7**. However, only in the more lipophilic *n*-Bu series was the potency of the cis isomer **7** greater than the potency of the corresponding aminoindene **2** when assessed against NE-induced contractions. Trans isomers **6** and **8**, however, were always less potent than their respective unsaturated analogues **1** and **2**. The observation that *cis*-**5** has reduced activity against KCl-induced contractions without altering its activity against NE-induced contractions could reflect a subtle change in the pharmacological mechanism of action, but further work is required to substantiate this possibility. In addition to possible subtle changes in the pharmacological mechanism, it may well be that selective antagonism of either KCl- or NE-induced contraction is a reflection of the relative sensitivity of the system to either the lipophilic nature or size of R. Clearly, when comparing tertiary or quaternary aminoindenes and aminoindans, the *n*-Bu analogues are always more potent than the *n*-Pr compounds, and overall the *cis*-*n*-Bu analogue **7** appears to be the most potent member of the series tested in this system.

Estimations of IC_{50} values are shown in Table I. These data indicate that, with the exception of the three quaternary compounds **3**, **4**, and **9**, all analogues tested were more potent inhibitors of KCl-induced than of NE-induced contractions. In vascular smooth muscle, agents that block inward Ca^{2+} transport across the cell membrane are more effective inhibitors of KCl- than of NE-induced contractions.[27,28] The differential effect is due to the fact that high K^+ depolarization stimulates Ca^{2+} influx, whereas most neurotransmitters and autacoids in addition release an intracelular Ca^{2+} store.[29,30] Thus, the data presented in Table I can be interpreted as indicative of inhibition by the aminoindenes and aminoindans of the voltage-dependent (KCl-mediated) and receptor-operated (NE-mediated) calcium channels in the smooth-muscle membrane, with possibly a greater effect on the voltage-dependent channels. This would be consistent with electrophysiological findings on cardiac muscle cells with **1** and **2**.[3] However, the greater potency of the aminoindenes and aminoindans against K^+-induced contractions than against NE-induced contractions observed in the present investigation (Table I) should be interpreted with caution, since the control tension generated by NE (0.98 ± 0.03 g) was greater than that generated by KCl (0.89 ± 0.05 g) and, therefore, the test compounds were working against a greater force in the case of NE-induced contractions.

The results of the present investigation are also compatible with the interpretation that the tertiary aminoindenes and aminoindans act, at least in part, as calcium

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antagonists at an intracellular site. Thus, as expected, the quaternary analogues were consistently less potent than the tertiary aminoindenes and the tertiary *cis*-aminoindans and only occasionally equipotent to the weak tertiary *trans*-aminoindans (Figures 1–4). Furthermore, whereas the aminoindenes and aminoindans were able to completely reverse the contractile effect of NE (Figures 2 and 4) as well as of KCl (Figures 1 and 3), we found that nifedipine (a selective inhibitor of membrane slow-channel Ca^{2+} influx[31,32]) completely reversed the effect of KCl but only reduced the effects of NE by a maximum of 65% even at high nifedipine concentration of 10^{-6} M (data not shown). Similar findings were reported for another membrane calcium-channel blocker, verapamil.[33] Additional substantiation of an intracellular site of action for the tertiary aminoindenes and aminoindans derives from a recent observation[34] that **2**, but not nifedipine, inhibited the contractile effects of U44069 (a stable analogue of PGH_2 which mobilizes intracellular calcium[35]) on the rat aorta in a calcium-free medium.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were obtained using a Bruker 90 MHz instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

2-*n*-Propyl- and 2-*n*-Butyl-3-(dimethylamino)-5,6-(methylenedioxy)ind-1-ene hydrochloride (1 and 2) were synthesized by the method of Witiak et al.[6] in 40 to 50% yield: mp 177–178 °C for both 1 and 2 (lit.[6] mp 177–178 °C for 1 and 2). Purity of compounds was assessed in part by TLC (acetonitrile/2-propanol, 1:1, plus 3 drops of glacial acetic acid per 10 mL of solvent).

***cis*-2-*n*-Butyl-1-(dimethylamino)-5,6-(methylenedioxy)indan Hydrochloride (7).** To a solution of **2** (4.0 g, 13.5 mmol) in 150 mL of absolute EtOH was added 150 mg of platinum(IV) oxide. This mixture was shaken for 20 h in contact with H_2 under pressure (50 lb/in.^{2}) and at room temperature. The platinum(IV) oxide was filtered by gravity, and the solvent was removed under reduced pressure, affording 3.9 g of off-white solid. Recrystallization with charcoal from absolute EtOH–Et_2O (1:20) yielded 2.32 g (59%) of snow-white compound **7**: mp 165–166 °C; TLC (MeOH/EtOAc, 3:7) showed one spot, R_f 0.30. Anal. ($C_{16}H_{24}NO_2Cl$) C, H, N.

***trans*-2-*n*-Butyl-1-(dimethylamino)-5,6-(methylenedioxy)indan Hydrochloride (8).** The filtrate from the recrystallization of the cis isomer (**7**) was concentrated under reduced pressure until a solid residue was obtained. This residue (1.05 g) was dissolved in a mixture of absolute EtOH (20 mL) and distilled H_2O (30 mL), made basic with 10% NaOH solution, and extracted with Et_2O (3 × 50 mL). The Et_2O layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oily residue (0.9 g) was chromatographed in 50 g of silica gel using EtOAc as eluent. A total of 24 fractions (15 mL each) were collected. Fractions 2–14 exhibiting compounds with R_f 0.49 by TLC with MeOH/EtOAc (3:7) were combined and concentrated under reduced pressure. The residual oil was dissolved in Et_2O (50 mL), after which gaseous HCl was passed through the resulting solution. A pale yellow solid (0.112 g) was obtained following gentle evaporation under reduced pressure. Recrystallization (with charcoal) from absolute EtOH/Et_2O (1:10) yielded 79 mg (2%) of white crystalline compound 8, mp 188–189 °C. Anal. ($C_{16}H_{24}NO_2Cl$) C, H, N.

***cis*-2-*n*-Propyl-1-(dimethylamino)-5,6-(methylenedioxy)indan hydrochloride (5)** was prepared using a procedure identical with that employed for the synthesis of **7**, yielding 1.37 g (68%) of white flakes: mp 184–185 °C; TLC (MeOH/EtOAc, 3:7) R_f 0.33. Anal. ($C_{15}H_{22}NO_2Cl$) C, H, N.

***trans*-2-*n*-Propyl-1-(dimethylamino)-5,6-(methylenedioxy)indan hydrochloride (6)** was prepared using a procedure identical with that employed for the synthesis of **8**, yielding 26 mg (1.3%) of white crystals: mp 187–188 °C; TLC (MeOH/EtOAc, 3:7) R_f 0.43. Anal. ($C_{15}H_{22}NO_2Cl$) C, H, N.

[2-*n*-Butyl-5,6-(methylenedioxy)inden-3-yl]trimethylammonium Iodide (3). Amine hydrochloride **2** (4.0 g, 13.6 mmol) was converted to the free base (10% NaOH solution), and the oily residue (3.42 g) was dissolved in absolute EtOH (100 mL) along with 6 mL (13.68 g, 96 mmol) of methyl iodide. The mixture was stirred at room temperature for 72 h in a dry atmosphere. The solvent and excess methyl iodide were removed under reduced pressure, affording 4.48 g of crude **3**. Recrystallization from absolute EtOH/Et_2O (3:7) yielded 3.2 g (59%) of **3** as pale yellow needles: mp 150–151 °C dec; TLC (10 mL of MeOH plus 3 drops glacial HOAc) R_f 0.14. Anal. ($C_{17}H_{24}NO_2I$) C, H, N.

[2-*n*-Propyl-5,6-(methylenedioxy)inden-3-yl]trimethylammonium Iodide (4) was prepared by a method identical with the one used to prepare **3**, yielding 1.41 g (52%) of reddish-brown crystals: mp 144–145 °C dec; TLC (under conditions used to develop **3**) R_f 0.18. Anal. ($C_{16}H_{22}NO_2I \cdot 0.5H_2O$) C, H, N.

[*cis*-2-*n*-Butyl-5,6-(methylenedioxy)indan-1-yl]trimethylammonium Iodide (10). Amine hydrochloride **7** (1.0 g, 3.5 mol) was converted to the free base (10% NaOH solution), and the isolated oily residue (0.86 g) was dissolved in absolute EtOH (50 mL) along with 2 mL (4.56 g, 0.032 mol) of methyl iodide. The mixture was stirred at room temperature for 75 h under a dry atmosphere, and the solvent and excess methyl iodide were removed under reduced pressure, affording 1.30 g of crude **10**. Recrystallization (charcoal) from absolute EtOH/Et_2O (5:5) yielded 0.54 g (42%) of compound **10**: mp 130–131 °C, above 200 °C dec; TLC (under conditions used to develop **3**) R_f 0.19. Anal. ($C_{17}H_{26}NO_2I \cdot 0.5H_2O$) C, H, N.

[*cis*-2-*n*-Propyl-5,6-(methylenedioxy)indan-1-yl]trimethylammonium Iodide (9) was prepared by a method identical with the one used to prepare **10**, yielding 0.43 g (48%) of crystals: mp 137–138 °C dec; TLC (under conditions used to develop **3**) R_f 0.17. Anal. ($C_{16}H_{24}NO_2I \cdot 0.5H_2O$) C, H, N.

NMR data are summarized in Tables II and III and confirm structural assignments, including the stereochemistry of analogues **5–10**. Assignments of chemical shifts for aryl proton resonance signals were based on the expected deshielding effect of the alkylamino groups on the nearest-neighbor aryl proton.

Observed vicinal couplings for J_{AB} (Table II) are consistent with the assigned structures. For cis coupling, J_{AB} = 0–2.25 Hz. For trans coupling, J_{AB} = 4.0–8.0 Hz. The NMR spectra are in accord with predictions for vicinal coupling constants based on the Karplus equation.[36] Thus, *cis*-aminoindans are expected to have J_{AB} = 0–2 Hz, owing to a dihedral angle of 70–90° resulting from rotation reflecting nonbonded interactions between dimethylamino and alkyl functions. J_{AB} for trans isomers should be 4–8 Hz, since the dihedral angle for the vicinal protons is 120–130°. Such J_{AB} values are easily observed for the H-1 proton resonance signal.

Pharmacology. Male Sprague–Dawley rats (Harlan Industries, Inc., Cumberland, IN), weighing 250–300 g, were sacrificed by cervical dislocation, and a 2.5-cm segment of the thoracic aorta was removed and rinsed in physiological buffer. Each aortic segment was cleaned of connective tissue and cut spirally to yield two 3 × 15 mm strips, and each strip was mounted isometrically under 1-g tension in a 10-mL tissue bath (37 °C) containing a normal physiological solution aerated with 5% CO_2 in O_2. Force generation was monitored using a Grass FT03 isometric transducer coupled to a Grass Model 7D polygraph recorder (Grass Instruments Co., Quincy, MA).

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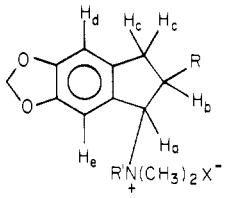
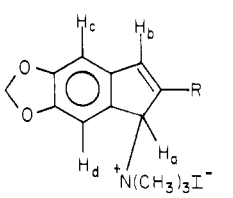
Table II. NMR Data for Various (Methylenedioxy)indan Hydrochlorides and Trimethylammonium Iodides



				chemical shift, δ, relative to Me_4Si in $CDCl_3$							
compd	R	R′	X⁻	H_aH_b	H_a	(R, H_b, $2H_c$)	H_d	H_e	OCH_2O	NCH_3	J_{ab}[a]
5	*n*-Pr	H	Cl^-	cis	4.36	3.34-0.94	6.69	7.34	5.99	2.62	0.0
5 (free base)	*n*-Pr			cis	3.98	3.23-0.94	6.64	6.99	5.94	2.42	2.25
6	*n*-Pr	H	Cl^-	trans	4.54	3.08-1.05	6.78	6.93	6.02	2.90-2.67	4.0
6 (free base)	*n*-Pr			trans	3.94	2.86-0.99	6.68	6.76	5.93	2.19	8.0
7	*n*-Bu	H	Cl^-	cis	4.37	3.51-0.90	6.69	7.35	5.99	2.63	0.0
8	*n*-Bu	H	Cl^-	trans	4.46	3.05-0.96	6.78	6.90	6.03	2.86-2.65	5.0
9	*n*-Pr	Me	I^-	cis	4.97	3.23-0.91	6.76	7.09	6.03	3.38	
10	*n*-Bu	Me	I^-	cis	4.92	3.22-0.88	6.76	7.07	6.03	3.37	

[a] Coupling constant determined from H_a splitting pattern (hertz).

Table III. NMR Data for 2-*n*-Butyl- (3) and 2-*n*-Propyl-5,6-(methylenedioxy)inden-3-yl (4) Substituted Trimethylammonium Iodides



		chemical shift, δ, relative to Me_4Si in $CDCl_3$						
compd	R	H_a	H_b	H_c	H_d	OCH_2O	$N(CH_3)_3$	R
3	*n*-Bu	5.65	6.59	6.65	7.14	5.94	3.49	2.63-0.91
4	*n*-Pr	5.64	6.68	6.75	7.26	6.03	3.57	2.76-1.00

After tissues had been allowed to equilibrate for 1 to 1.5 h in normal physiologic solution, tissue contraction was induced by introducing either 1×10^{-7} M NE or 40 mM KCl buffer to the tissue bath. Under these conditions, both NE and KCl induce a tissue contraction which reaches maximum tension generation within 30 min and which is maintained for many hours. The spasmolytic activity of each test compound was then assessed by adding it in increasing concentrations to the solution bathing the tissue and monitoring the resulting degree of tissue relaxation until a maximum effect had been obtained or for a maximum period of 30 min. The test compound was then washed out, and the control response to NE or KCl was regained.

Tissue tension at each concentration of aminoindan or aminoindene was expressed as a percentage of the control tension generated by NE and KCl prior to addition of these test compounds. Separate preliminary experiments were performed to determine the degree of tissue relaxation (loss of tension) due to time-dependent tissue fatigue, and the value of the control tension generated by NE and KCl prior to the addition of test compounds was appropriately adjusted whenever the duration of the experiment was such that fatigue could be expected to cause greater than a 6% loss of tension. Control tension generation to NE and KCl was 0.98 ± 0.03 and 0.89 ± 0.05 g, respectively. These values represent 85.1 and 84.2% of the maximum induceable contractions with these agonists, respectively. All concentrations cited represent final tissue bath concentrations.

Concentration vs. percent response data obtained from each tissue was transformed to its appropriate probit value, and IC_{50} values were then estimated using linear regression analysis.

The normal physiological solution was composed of (g/L): NaCl, 6.9; KCl, 0.35; $MgCl_2 \cdot 6H_2O$, 0.11; NaH_2PO_4, 0.138; $NaHCO_3$, 2.1; EDTA, 0.01; $CaCl_2 \cdot 2H_2O$, 0.368; dextrose, 2.0. High potassium buffers were made by substituting KCl for NaCl on an equimolar basis to maintain tonicity.