°C (from EtOAc-cyclohexane); *m/e* 291. Anal. ($C_{16}H_{21}NO_2S$) C, H, N. (3) Hydroxylamine **78**: 0.72 g; mp 255 °C (from EtOAc-cyclohexane); *m/e* 307. Anal. ($C_{16}H_{21}NO_3S$) C, H, N.

Amides, Carbamates, and Ureas from 4-(Adamantyloxy)anilines (Table VI). Method G. Acetylation was conducted using Ac_2O as previously described.[2]

Method H. A solution of 5.7 mmol of the aniline in 15 mL of ice-cold pyridine was treated with an excess of the appropriate acid halide. Following 18 h of standing at room temperature the mixture was diluted with water, precipitating the product.

Method I. To an ice-cooled solution of the amine (7.8 mmol) and 1.08 g of Et_3N in 40 mL of THF there was added 1.1 equiv of the acid chloride. Following 3 h of stirring at room temperature the solvent was removed in vacuo and the mixture worked up as in method H.

Method J. A solution of 0.82 mol of the aniline and an excesss of the heterocumulene in 40 mL of THF was allowed to stand at room temperature overnight. The mixture was diluted with water, precipitating the product.

Method K. A suspension of 41 mmol of the aniline in 60 mL of ethyl formate was stirred at reflux for 48 h. The mixture was taken to dryness.

***N*-(1-Adamantyl)-*N*,*N*'-(1,4-phenylene)bis[acetamide] (72).** The diamine (**70**, 2.86 g) was acetylated by method G. There was obtained 1.90 g of product (32%): mp 245–346 °C. Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

***N*-[(Adamantyl-X)phenyl]pyrrolidines** (Table VII) were prepared as previously described.[2]

Secondary and Tertiary Amines Derived from 4-(1-Adamantyloxy)anilines (Table VIII). Method L. $LiAlH_4$ reductions were conducted as previously described.[2]

Method M. To an ice-cold solution of 4.8 mmol of the amide in 20 mL of THF there was added 10 mL of 1 N B_2H_6 in THF. Following 18 h of standing in the cold there was added 1 mL of H_2O. The bulk of the solvent was then removed in vacuo and the residue stirred for 5 h with 40 mL of 2.5 N HCl. The mixture was then made strongly basic and extracted with Et_2O. The extract was taken to dryness and the residue treated with ethereal HCl.

Method N. A mixture of 7.9 mmol of the amine, 1.07 g of K_2CO_3, and 8 mmol of the halide in 10 mL of DMF and 40 mL C_6H_6 was heated at reflux for 17 h. The mixture was allowed to cool, washed with water and brine, and taken to dryness.

Method O. To a solution of 7.8 mmol of the secondary amine in 20 mL of THF cooled in an ice–MeOH bath there was added 4.75 mL of 1.64 N BuLi in pentane. A solution of 1 equiv of a 1:1 mixture of the chloroamine and toluene in 20 mL of THF was then added. The mixture was stirred in the cold for 1 h and at reflux for 18 h. The mixture was allowed to cool and then worked up as in method M.

***N*-Methyl-α-(1-adamantyl)-*p*-toluidine Hydrochloride (63).** The free base from amine **62** (2.77 g, 10 mmol) was converted to the carbamate by method H. There was obtained 1.68 g of product (SSB): mp 130–132 °C. Anal. ($C_{20}H_{27}NO_2$) C, H, N.

This was reduced by means of $LiAlH_4$ and the product worked up as in method L. The gum was chromatographed on silica gel (30% CH_2Cl_2–SSB/NH_4OH) and converted to the hydrochloride salt. There was obtained 0.15 g (CH_2Cl_2–EtOAc) of **63**: mp 208–210 °C. Anal. ($C_{18}H_{26}ClN$) H, N; C: calcd, 71.85; found, 71.41.

***p*-(2-Adamantyloxy)-*N*-methylaniline Hydrochloride (86).** The carbamate **85** (2.0 g, 6.4 mmol) was reduced and worked up as in method L. The gum was chromatographed as above and the product recrystallized (MeOH–Et_2O) as its hydrochloride salt. There was obtained 0.71 g (38%) of **86**: mp 223–227.5 °C. Anal. ($C_{17}H_{24}ClNO$) C, H, N.

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2-Indanpropionic Acids: Structural Leads for Prostaglandin $F_{2\alpha}$ Antagonist Development[1]

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A rationale is presented for the development of prostaglandin $F_{2\alpha}$ receptor antagonists. The target analogue, 5,6-(dibenzyloxy)-1-oxo-2-propyl-2-indanpropionic acid (**3**), was shown to have selective activity for antagonism of $PGF_{2\alpha}$ when compared to the antagonism of acetylcholine and KCl on the mouse ileum, whereas other 2-indanpropionic acids (**1**, **2**, **4**), not substituted with benzyl functions, were considerably less active and nonselective. The results suggest that **3** may serve as a lead compound for further drug development.

H_1-receptor antihistamines generally have basic amino functions, presumably capable of interacting with an anionic site as does histamine, but also have two aryl groups, generally β or γ to the amino function, which replace the imidazole ring of the agonist and are thought to provide increased affinity with a loss of intrinsic activity.[2-4] Hence, we reasoned[5] that antiprostaglandins might be constructed having carboxyl groups capable of interacting with a cationic site. Aryl functionality located approximately at the position of the cyclopentanediol grouping of $PGF_{2\alpha}$ similarly might be expected to provide increased affinity with a loss of intrinsic activity during receptor binding.[5] Thus, for our preliminary studies a series of carboxylic acids (**1**–**4**) was synthesized and

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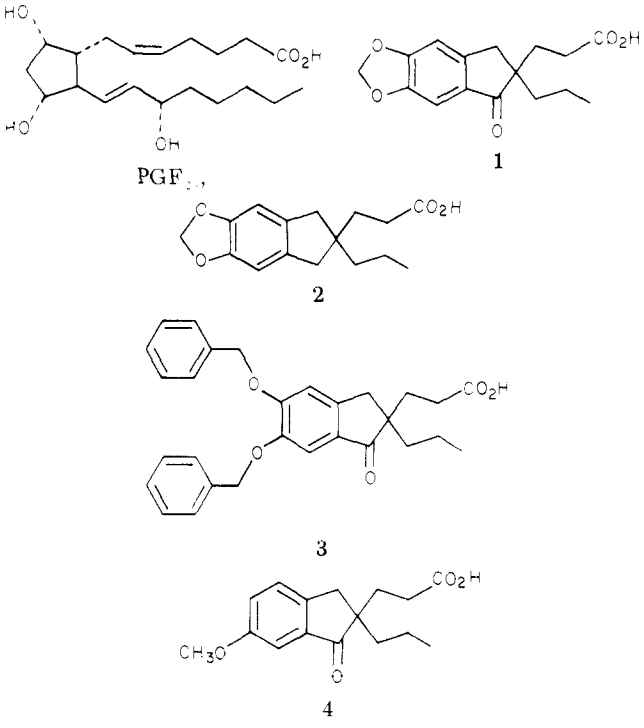
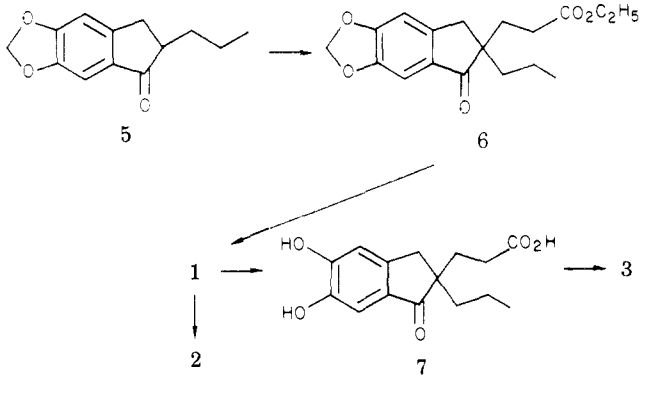


evaluated for selective antagonist activity against $PGF_{2\alpha}$, acetylcholine (AcCh), or KCl on the mouse ileum. Analogue development involving **1**–**3** was of particular interest owing to their facile preparation from dimethylaminoindene intermediates obtained using the Vilsmeier–Haack cyclization reaction.[6] Furthermore, the keto function in **1**, **3**, and **4** has a juxtaposition to the carboxyl group similar to the juxtaposition of the 15α-hydroxyl function to the carboxyl group of $PGF_{2\alpha}$ in the extended conformation. Pharmacological investigations indicate that the target analogue **3** may serve as a prototype for future drug development and construction of selective antagonists for prostaglandins.

Synthetic Aspects. Indanone **5**, synthesized according



to Witiak et al.,[6] underwent facile Michael addition of ethyl acrylate affording indanone ester **6** in 86% yield. Alkaline hydrolysis to yield **1** followed by Clemmenson reduction afforded **2** in excellent yield. Available methods for methylenedioxy cleavage using BCl_3[8] and PCl_5[9] proved to be unsatisfactory owing to the instability of catechol **7** under the reaction conditions. Under Bick and Russel[10] modifications, PCl_5-induced methylenedioxy cleavage afforded **7** in 71% yield. Catechol **7** required storage under N_2 to prevent air oxidation and brown discoloration. Treatment of **7**, under N_2, with K_2CO_3–$C_6H_5CH_2Br$ in refluxing acetone for 50 h gave the dibenzyl ether ester, which was not isolated but was immediately hydrolyzed to the acid **3** which was isolated in 39% yield.

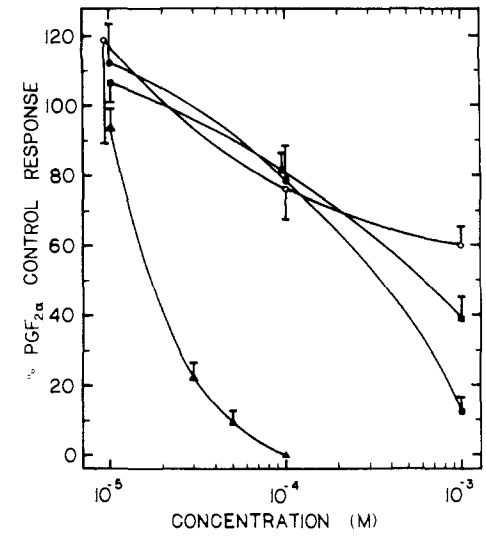
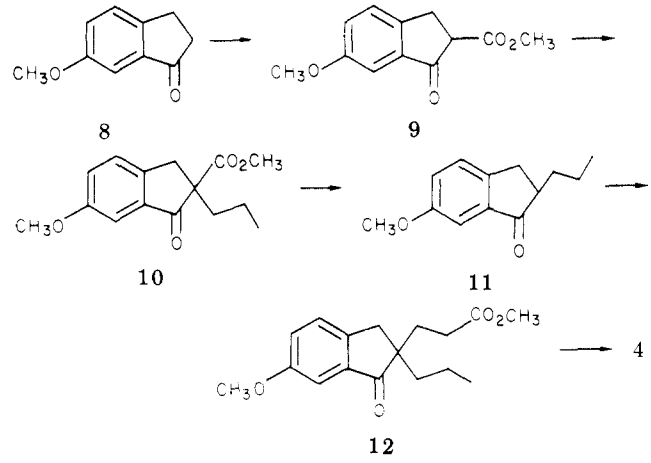


Figure 1. The effect of various concentrations of compounds **1**–**4** (*x* axis) on $PGF_{2\alpha}$-induced contraction of the isolated mouse ileum: (○ ○) **1**, (● ●) **2**, (▲ ▲) **3**, (■ ■) **4**.

Although compound **5** could be prepared from a Vilsmeier–Haack aminoindene intermediate, indanone **11** (a precursor needed for the elaboration of **4**) was inaccessible by this route due to the failure of the requisite intermediate to cyclize in the absence of para activation.[6] Thus, **4** was prepared from 6-methoxy-1-indanone (**8**).[11] Con-



densation of **8** with dimethyl carbonate in the presence of NaH afforded carbomethoxy analogue **9** in 95% yield. 2-Alkyl-substituted indanones only could be prepared in poor yield (10–15%) from **8** via the enamine. Also, alkylation of **9** using Na–*n*-PrI or NaOEt–*n*-PrI in EtOH afforded poor yields (<5%) of **10**. Alternatively, use of NaH–*n*-PrI in freshly distilled THF containing HMPA afforded **10** in 67% yield. In the absence of HMPA, yields were drastically lower. Hydrolysis of **10** and subsequent decarboxylation in HOAc–concentrated HCl–H_2O (2.5:1:1) afforded indanone **11** in 78% yield. Anion formation using *t*-BuOK in *t*-BuOH followed by Michael addition to methyl acrylate yielded indanone ester **12** in crude form after column chromatography on silica gel–$CHCl_3$. Alkaline hydrolysis of ester **12** afforded keto acid **4** in 54% yield based on **11**.

Pharmacological Results and Discussion. The results of the preliminary pharmacological evaluation are depicted in Figures 1–3. At the high concentration of 10^{-3} M of the test compounds (**1**–**4**), varying degrees of inhibition of the spasmogenic action of the agonists ($PGF_{2\alpha}$, AcCH, and KCl) are seen with all four test compounds; compound **3** proved to be the most effective antagonist.

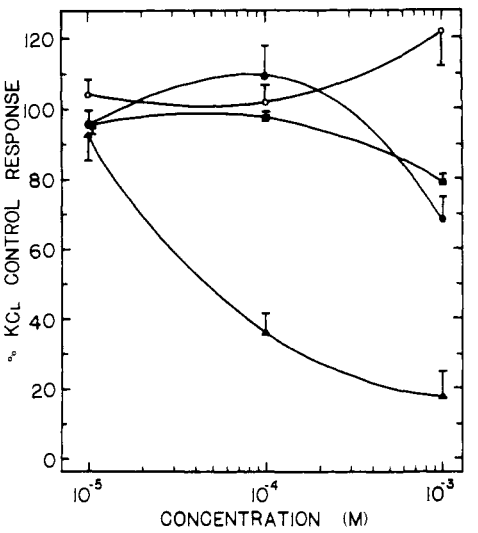


Figure 2. The effect of various concentrations of compounds 1–4 (*x* axis) on acetylcholine-induced contractions of the isolated mouse ileum: (○–○) 1, (●–●) 2, (▲–▲) 3, (■–■) 4.

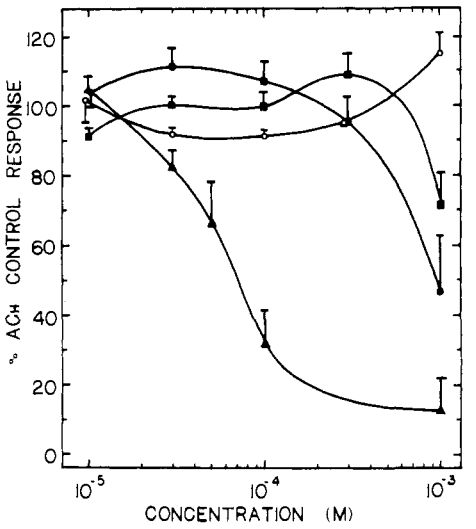


Figure 3. The effect of various concentrations of compounds 1–4 (*x* axis) on KCl-induced contractions of the isolated mouse ileum: (○–○) 1, (●–●) 2, (▲–▲) 3, (■–■) 4.

However, at the 10^{-4} M concentration, compounds **1**, **2**, and **4** did not block the effect of AcCh or KCl and only marginally inhibited (by 20%) the action of $PGF_{2\alpha}$. On the other hand, compound **3** at 10^{-4} M completely blocked the action of $PGF_{2\alpha}$ (Figure 1) and significantly reduced (by approximately 70%) the spasmogenic actions of AcCh and KCl (Figures 2 and 3). More importantly, at concentrations below 10^{-4} M when compounds **1**, **2**, and **4** had no antagonistic action against any of the agonists, compound **3** exhibited antagonist properties against AcCh, KCl, and, more significantly, against $PGF_{2\alpha}$. Thus, at a concentration of 5×10^{-5} M, compound **3** produced a 90% inhibition of the spasmogenic action of $PGF_{2\alpha}$ (Figure 1) and only a 50% inhibition of KCl (Figure 3) and a 35% inhibition of AcCh (Figure 2). At a concentration of 3×10^{-5} M, compound **3** produced an 80% inhibition of the spasmogenic action of $PGF_{2\alpha}$ (Figure 1), whereas the action of AcCh was blocked by less than 20% (Figure 2) and KCl was blocked by 40% (Figure 3). The antagonism produced by all of the test compounds (**1**–**4**) was reversible (see Experimental Section).

It is clear from the data presented that compound **3** is the most potent antagonist of the series of carboxylic acids (**1**–**4**) when tested against $PGF_{2\alpha}$, AcCh, and KCl in the isolated mouse ileum preparation. Furthermore, the antagonistic action of compound **3** seems to be more selective for $PGF_{2\alpha}$ as compared to AcCh or KCl. Hopefully structural modification of compound **3** with conversion of the keto group to a hydroxyl group will enhance the specificity of the antagonism against $PGF_{2\alpha}$. Investigations currently in progress are defining the activity of compound **3** and certain hydroxyl derivatives on the uterus, since the ultimate purpose of this project is the development of prostaglandin $F_{2\alpha}$ receptor antagonists which may have a potential value as antiabortifacients. Likewise, a comparison of the pharmacological properties of compound **3** and its derivatives with already existing prostaglandin receptor antagonists[12] will be undertaken.

The PG receptor antagonists currently available belong to chemically unrelated classes. These are the 7-oxaprostaglandins,[13] the dibenzoxazepine hydrazides,[14] and certain polymers,[15] monomers, and dimers[16] of phloretin phosphate, as well as the phenyl phosphonates[17] and the fenamates[18]. Bennett[12] has exhaustively reviewed the pharmacology of these presumed PG receptor antagonists on a multitude of in vitro and in vivo systems and emphasized the need for the development of more active and more selective inhibitors of the myriad actions of the prostaglandins.

Experimental Section

Chemistry. For obtaining physical data on our compounds the following instruments were employed: melting points, calibrated Thomas-Hoover apparatus; IR spectra, Perkin-Elmer 257 and Beckman IR 4230 spectrophotometers; GLC, Hewlett-Packard 402 biomedical gas chromatograph; NMR spectra, Varian A-60A and Bruker HX-90E spectrometers. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Ethyl 5,6-(Methylenedioxy)-1-oxo-2-propyl-2-indanpropionate (6). To a solution of 2.18 g (0.01 mol) of **5** and 0.112 g (0.001 mol) of *t*-BuOK in 25 mL of *tert*-butyl alcohol was added dropwise, with stirring and under a N_2 atmosphere, 1.2 g (0.012 mol) of ethyl acrylate. The resulting solution was stirred at room temperature for 90 min, acidified with HOAc, concentrated under reduced pressure, and diluted with Et_2O. The Et_2O solution was washed twice with aqueous Na_2CO_3 solution, dried (Na_2SO_4) and concentrated under reduced pressure, affording 2.78 g (87%) of a viscous oil which was purified by distillation yielding a colorless oil: bp 188–190 °C (0.15 mm); IR 1690 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.08 (s, 1 H, aromatic), 6.81 (s, 1 H, aromatic), 6.05 (s, 2 H, $-OCH_2O-$), 4.09 (q, 2 H, $-CH_2-$ ester, J = 7 Hz), 2.89 (s, 2 H, geminal), 0.68–2.43 (m, 14 H, aliphatic; contains a triplet $-CH_3$ of ester; J = 7 Hz). Anal. ($C_{18}H_{22}O_5$) C, H.

5,6-(Methylenedioxy)-1-oxo-2-propyl-2-indanpropionic Acid (1). A solution of NaOH (10.0 g) in 100 mL of MeOH–H_2O (15:85) was added to 1.66 g (0.005 mol) of **6**. The mixture was stirred at room temperature overnight, diluted with H_2O, and extracted with two 100 mL portions of Et_2O. The aqueous layer was acidified with 2 N HCl and extracted with three 100 mL portions of Et_2O. The combined Et_2O layers were dried (Na_2SO_4) and evaporated to give an oil. The oil was stirred overnight with hexane, affording a pale-yellow solid which was crystallized from benzene–hexane, yielding 1.4 g (93%) of white needles: mp 91–92 °C; IR 3400, 1710, and 1693 cm^{-1}; NMR ($CDCl_3$) δ 9.07 (s, 1 H, CO_2H exchangeable with D_2O), 7.1 (s, 1 H, aromatic), 6.8 (s, 1 H, aromatic), 6.05 (s, 2 H, $-OCH_2O$), 2.9 (s, 2 H, geminal), 0.66–2.5 (m, 11 H, aliphatic). Anal. ($C_{16}H_{18}O_5$) C, H.

5,6-(Methylenedioxy)-2-propyl-2-indanpropionic Acid (2). A mixture of 20 g of mossy Zn, 1.5 g of $HgCl_2$, 2 mL of concentrated HCl, and 20 mL of H_2O was stirred for 5 min. The aqueous solution was decanted and the amalgamated Zn was covered with 20 mL of H_2O and 16 mL of concentrated HCl. A solution of 1 g (0.0034 mol) of **1** in 25 mL of sulfur-free toluene was added to the amalgamated Zn along with 2 mL of glacial HOAc. The mixture was refluxed for 24 h, during which time 6 mL of concentrated HCl was added approximately every 5 h. The solution was cooled to room temperature (the aqueous layer

separated) and, after dilution with H_2O, was extracted with three 75-mL portions of Et_2O. The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure, affording 0.8 g (84%) of a viscous oil, bp 193–194 °C (0.05 mm). The purified distillate afforded white crystals: mp 81–82 °C; IR 3580, 3300, and 1710 cm^{-1}; NMR ($CDCl_3$) δ 9.63 (s, 1 H, CO_2H), 6.56 (s, 2 H, aromatic), 5.83 (s, 2 H, $-OCH_2O-$), 2.63 (s, 4 H, benzylic), 0.76–2.5 (m, 11 H, aliphatic; two virtually symmetrical multiplets). Anal. ($C_{16}H_{20}O_4$) C, H.

5,6-Dihydroxy-1-oxo-2-propyl-2-indanpropionic Acid (7). Dry benzene (90 mL) was added to a mixture of 1.16 g (0.004 mol) of **1** and 3.34 g (0.016 mol) of PCl_5. The resulting solution was maintained under N_2 and heated at reflux for 9 h. After evaporation to dryness, the residual oil was stirred with 150 mL of H_2O for 12–14 h. The resulting suspension was refluxed on an oil bath for an additional 3 h. The hot solution was filtered into a round-bottom flask wrapped in aluminium foil and was stored overnight in the dark. Upon standing, 0.8 g (71.4%) of white needles, mp 85–87 °C, was obtained. This product was extremely sensitive to light and decomposed on standing: NMR (acetone-d_6) δ 7.09 (s, 1 H, aromatic), 6.93 (s, 1 H, aromatic), 2.91 (s, 2 H, benzylic), 0.65–2.41 (m, complex, 11 H, aliphatic); mass spectrum *m/e* (rel intensity) 163 (14), 164 (11), 175 (17), 176 (13), 177 (100), 178 (11), 189 (19), 218 (23), 236 (83), 237 (10), 261 (13), 278 (8). Anal. ($C_{15}H_{18}O_5$) C, H.

5,6-Bis(benzyloxy)-1-oxo-2-propyl-2-indanpropionic Acid (3). To a solution of 0.6 g (0.0019 mol) of **7** and 1.0 g of K_2CO_3 in 50 mL of dry acetone was added dropwise, with stirring and under N_2, 1.30 g (0.0073 mol) of benzyl bromide. The resulting mixture was refluxed under N_2 for 50 h, after which time the solution was filtered to remove K_2CO_3. The K_2CO_3 solids were washed with acetone, and the combined solutions were concentrated under reduced pressure, affording an oil which was partitioned between benzene and 1 N NaOH. The benzene layer was dried and concentrated under reduced pressure, affording an oil which was hydrolyzed with 10% KOH solution in the usual manner. The oil obtained after reaction workup was stirred with *n*-hexane, yielding a white solid. Recrystallization from benzene–hexane afforded 0.38 g (39%) of white crystals: mp 109–110 °C; IR 3300, 1720 (broad) cm^{-1}; NMR ($CDCl_3$) δ 7.21–7.58 (m, 12 H, aromatic and 1 CO_2H), 6.9 (s, 1 H, aromatic), 5.21 (s, 2 H, $PhCH_2O-$), 5.14 (s, 2 H, $PhCH_2O-$), 2.87 (br, 2 H, indanone benzylic H), 0.66–2.5 (m, 11 H, aliphatic). Anal. ($C_{36}H_{36}O_5$) C, H.

2-(Carbomethoxy)-6-methoxy-1-indanone (9). To a slurry of 3.4 g (0.04 mol; 57% emulsion) of NaH in 10 mL of dimethyl carbonate (freshly distilled from NaH) was added, with stirring under N_2, a solution of 6.48 g (0.018 mol) of 6-methoxy-1-indanone (**8**) in 70 mL of dimethyl carbonate. The mixture was refluxed for 3 h, after which time the excess NaH was decomposed by the dropwise addition of ice-cold H_2O followed by acidification with glacial HOAc. The solution was extracted with Et_2O, and the Et_2O layer was concentrated under reduced pressure, affording an oil which was chromatographed on Florisil with $CHCl_3$ yielding 8.4 g (95.6%) of a yellow solid. A small portion of this solid was purified by recrystallizing from MeOH, affording white crystals: mp 78–79 °C, lit.[19] mp 79–79.5 °C; IR 1710 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 7.03–7.51 (m, 3 H, aromatic), 3.28–4.0 (m, 9 H, 2 H-3, H-2, and two sharp singlets for CO_2CH_3 and OCH_3). Anal. ($C_{12}H_{12}O_4$) C, H.

2-(Carbomethoxy)-2-propyl-6-methoxy-1-indanone (10). To a slurry of 0.8 g (0.018 mol; 57% emulsion) of NaH in 10 mL of THF (freshly distilled from $LiAlH_4$) was added, with stirring under N_2, a solution of 4.0 g (0.018 mol) of **9** in 50–60 mL of THF. The mixture was heated at 60–70 °C for 15 min, and 3 mL of *n*-propyl iodide was added. The mixture was refluxed for 5 h and cooled, and 15 mL of hexamethylphosphoramide was added. The clear solution was stirred at room temperature for 1 h and refluxed overnight. The solution was concentrated under reduced pressure and partitioned several times between H_2O and Et_2O, and the organic layer was concentrated under reduced pressure, affording a light-brown oil which was chromatographed on Florisil with $CHCl_3$, affording 3.18 g (66.8%) of yellow oil which was purified by microdistillation using a bath temperature of 116–117 °C (0.05 mm): IR 1710 and 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.08–7.5 (m, 3 H, aromatic), 3.82 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, OCH_3), 3.64 (δ_A), 3.03 (δ_B, 2 d, 2 H, benzylic, J_{AB} = 17.4 Hz), 0.71–2.23 (m, 7 H aliphatic). Anal. ($C_{15}H_{18}O_4$) C, H.

2-Propyl-6-methoxy-1-indanone (11). A solution (25 mL) of concentrated HCl and H_2O (1:1) was added to a solution of 4.6 g (0.017 mol) of **10** in 40 mL of glacial HOAc. The mixture was refluxed for 5 h. Concentrated HCl (5 mL) was added, and the solution was stirred overnight at room temperature. The reaction mixture was extracted with three 100-mL portions of Et_2O, and the combined Et_2O layers were concentrated under reduced pressure, affording a yellow oil which was chromatographed on silica gel with $CHCl_3$, yielding 2.8 g (78%) of oil which solidified under reduced pressure. A small portion of this oil was distilled with a bath temperature of 95–96 °C (0.025 mm), affording a white solid: mp 50–51 °C; IR 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.03–7.46 (m, 3 H, aromatic), 3.83 (s, 3 H, OCH_3), 2.45–3.43 (m, 3 H, ABC pattern of 2 H-3 and H-2) and 0.76–2.16 (m, 7 H, aliphatic). Anal. ($C_{13}H_{16}O_2$) C, H.

6-Methoxy-1-oxo-2-propyl-2-indanpropionic Acid (4). Analogue **4** was prepared from 2.04 g (0.01 mol) of **11** and 1.03 g (0.012 mol) of methyl acrylate in the presence of *tert*-butyl alcohol according to the method described for the preparation of **1** from **5**, except that the reaction mixture was stirred at room temperature for 90 min. After distillation, 2.4 g of the viscous oil **12** was obtained which was not further purified. Hydrolysis of **12** using 15% methanolic KOH (80:20 H_2O–MeOH) afforded a yellow semisolid, which was crystallized from benzene–hexane to yield 1.5 g (54.3%) of white needles: mp 96–97 °C; IR 1740 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 8.46 (1 H, CO_2H exchangeable with D_2O), 7.41–7.05 (m, 3 H, aromatic), 3.82 (s, 3 H, OCH_3), 2.92 (br, 2 H, benzylic), 0.66–2.5 (m, 11 H, aliphatic). Anal. ($C_{16}H_{20}O_4$) C, H.

Pharmacological Methods. The methods were similar to those described previously by Rahwan et al.[20] Briefly, female albino mice (20–25 g) were sacrificed by cervical dislocation, and sections of the ileum were prepared for isotonic contraction recordings under 200 mg of tension in 10 mL tissue baths containing a bathing solution (37 °C) having the following composition (g/L): NaCl, 6.90; KCl, 0.35; $CaCl_2 \cdot 2H_2O$, 0.37; $MgCl_2 \cdot 6H_2O$, 0.11; $NaH_2PO_4 \cdot H_2O$, 0.14; $NaHCO_3$, 2.10; dextrose, 2.0. Recordings were made with an isotonic MKII myograph transducer and a Physiograph 4 recorder (E&M Instrument Co., Houston, Texas). The bathing solution was aerated with 5% CO_2 in O_2. A 30-min equilibration time was allowed prior to all experiments.

In each experiment, a control response to $PGF_{2\alpha}$ (10^{-7} M bath concentration), acetylcholine (AcCh; 10^{-6} M bath concentration), or KCl (54 mM bath concentration) was obtained, and the bath was then washed three times prior to incubation of the tissue with any of the test compounds (**1**–**4**). The test compound was added to the bath and left in contact with the ileum for 3 min. $PGF_{2\alpha}$ (10^{-7} M), AcCh (10^{-6} M), or KCl (54 mM) was then added to the bath, and the contractions were recorded. After 5 min, the bath was washed three times, and the control response to $PGF_{2\alpha}$, AcCh, or KCl was regained. All values were calculated as percent of the control responses to $PGF_{2\alpha}$, AcCh, or KCl.

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Relationship of Nonspecific Antiarrhythmic and Negative Inotropic Activity with Physicochemical Parameters of Propranolol Analogues

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In an attempt to separate the nonspecific antiarrhythmic activity of propranolol from its negative inotropic effects, analogues containing hydrophilic and lipophilic substituents on the nitrogen and on the naphthyl ring were prepared and tested in an isolated tissue preparation. Though it had been predicted that analogues containing a very hydrophilic group on the nitrogen would have the highest antiarrhythmic/negative inotropic effect ratio, it was found that both effects increased identically when the lipophilicity of either the nitrogen or ring substituent was increased.

Compounds can exhibit antiarrhythmic activity by a variety of different mechanisms.[1] A number of compounds have antiarrhythmic activity associated with membrane stabilizing properties, and these are often referred to as nonspecific in their action and include such drugs as quinidine, procainamide, lidocaine, and propranolol in high doses.[2,3] These compounds are thought to exert their antiarrhythmic action by altering the physicochemical properties of the lipid bilayer of the cardiac sarcolemma, thereby interfering with the operation of the ion channel through which depolarizing current flows.[1]

With regard to the structure–activity relationships of the nonspecific antiarrhythmic agents, most of the compounds contain a secondary or tertiary amine group that is separated by two or three carbons from a second group that is capable of hydrogen bonding (e.g., alcohol, ester, and amide).[2] There is also a lipophilic aromatic group adjacent to the hydrogen-bonding group. It is thought that the lipophilic aromatic ring penetrates into the bilayer of the cell membrane, thereby altering its physicochemical properties, while the protonated nitrogen interacts with some polar group at the exterior of the membrane, possibly displacing calcium ion.[2] The net result of these interactions is to decrease the conductance of the membrane to depolarizing ions.

In addition to antiarrhythmic activity, these compounds also decrease cardiac contractility. There is some evidence to indicate that at least a part of the negative inotropic activity is due to intracellular events.[4,5] Besch and Watanabe[5] suggested that the decrease in contractility produced by nonspecific antiarrhythmic agents was due to depletion of calcium stores in the cardiac sarcoplasmic reticulum. However, Langer[6] suggested that the sarcoplasmic reticulum served only as a mechanism for removal of calcium ions after the contractile process. He proposed a carrier for calcium in the sarcolemma as the source of contractile calcium ions.

Therefore, while it is generally accepted that the site of action for nonspecific antiarrhythmic activity is at the external surface of the cardiac cell membrane, there is considerable disagreement as to the site of action for the negative inotropic activity. If the antiarrhythmic and negative inotropic activities are due to separate mechanisms, it should be possible to separate the two activities and synthesize antiarrhythmic agents devoid of negative inotropic actions. Baird and Hardman[7] found a direct correlation between the concentration of nonionized procaine and negative inotropic activity in the isolated turtle heart ventricle. Procaine ethochloride, a quaternary salt, exhibited the same qualitative effects on conduction time as did procaine, but the quaternary salt lacked negative inotropic activity. This appears to support the contention that the ability to cross the sarcolemma is important in determining the effect on contractility.

Hellenbrecht et al.[8] demonstrated that, for a series of β-adrenergic blocking agents, the ability to alter myocardial conduction velocity could be correlated with physicochemical parameters such as hydrophobicity (log P) and surface activity. The compounds tested were ring-substituted compounds and it was demonstrated that increasing the polarity of the aromatic ring decreased the effect on conduction velocity. In a further study, Hellenbrecht et al.[9] evaluated the effect of two series of β-adrenergic blockers on conduction velocity in the frog heart and cardiac contractility in an in vivo cat preparation. The compounds studied were both ring-substituted (alkyl substituents) and N-substituted (alkyl substituents) and encompassed a wide range of hydrophobicities. They found that both conduction velocity and contractility could be linearly correlated with the hydrophobicity of the

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