Synthesis and Smooth Muscle Relaxant Activity of a New Series of Potassium Channel Activators: 3-Amido-1,1-dimethylindan-2-ols

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The synthesis of a novel series of smooth muscle relaxants which have been shown to act via the opening or activation of potassium channels is described. Compounds have been evaluated for their ability to inhibit spontaneous tone in guinea pig isolated trachealis and structure-activity relationships are discussed. One compound in particular, 1,1-dimethyl-5-nitro-3-(2-pyridon-1-yl)indan-2-ol, (16) was identified as a potent relaxant of airways smooth muscle in vitro with $IC_{50} = 0.15 \ \mu M$ and was found to significantly inhibit histamine-induced dyspnoea in conscious guinea pigs when given orally 30-45 min prior to challenge.

Introduction

Potassium channel activators, or openers, have attracted considerable attention because of evidence for their potential value in the treatment of those disorders in which smooth muscle contraction is involved.¹ Particular applications include asthma, hypertension, and urinary incontinence, and many compounds have shown effectiveness in models of hypertension.² The potential of the potassium channel activators in asthma has been less well studied, but one class of compounds, the dihydrobenzopyrans,³ of which cromakalim (1) is the prototype, has been shown to be potent relaxants of guinea pig isolated trachealis in vitro.⁴ Detailed evaluation of cromakalim and its active (3S,4R) enantiomer BRL 38227 have demonstrated the ability of these compounds to prevent bronchospasm in vivo when administered either orally⁵ or by inhalation.⁶ Furthermore, limited studies with cromak-



alim in asthmatics have demonstrated its effectiveness in the alleviation of the nocturnal manifestations of the disease.⁷ Clinical studies are currently underway with BRL 38227 both in asthma and in hypertension.

As a result of our interest in the respiratory effects of the potassium channel activators, we have evaluated several structural variants of cromakalim and its congeners. Of particular interest were the indanols 7-20, arising from ring contraction of the dihydropyran ring, since overlap studies suggested that these compounds would occupy a similar spatial volume. This paper discusses the synthesis

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^aReagents: (i) KBH₄, MeOH; (ii) *p*-TSA, PhH, reflux; (iii) NBS, H₂O, DMSO; (iv) *m*-CPBA, DCM; (v) pyrrolidinone, piperidone, or pyridone, KOBu^t, heat; (vi) MeSO₂Cl, NEt₃, THF; (vii) KOBu^t.

and biological activity of this novel series of potassium channel activator.

Chemistry

The general synthetic strategy for the preparation of the 3-amidoindanols 7-20 (Table I) and 3-amidoindenes 26-29 (Table II) follows the route outlined in Scheme I (only relative stereochemistry shown). The requisite indanones 2a-d were readily prepared in reasonable yield according to published procedures,⁸ and the 5-amino compound 2b was subsequently converted into the corresponding 5-cyano 2e and 5-iodo 2f derivatives by using the Sandmeyer reaction. Reaction of copper(I) cyanide with 2d in hot DMF afforded 88% of the 6-cyano compound 2g. Reduction of 2a-g with potassium borohydride in MeOH resulted in

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Table I. 3-Amidoindan-2-ols



| | | | | • | | | | | |
|------------|-------------------|----|---|----------------------|-------------|---|----------------|---------|---|
| compd | R | R1 | n | mp, °C | yield, % | formula | anal. | methodª | inhibition of spontaneous tone in guinea pig tracheal spirals ^b |
| cromakalim | | | | | | | | | $1.1 (0.06 - 1.9); 0.89 \pm 0.02; 7$ |
| BRL 38227 | | | | | | | | | $0.49 (0.36 - 0.67); 0.88 \pm 0.02; 10$ |
| 7 | 5-NO2 | Me | 1 | 222-223 | 24 | C15H18N2O4 | C.H.N | Α | $2.80 (1.66-4.74); 0.88 \pm 0.03; 6$ |
| 8° | 5-NO | Me | 1 | 144-145 | 24 | C15H18N2O | C.H.N | Α | >20; 0.26; 2 |
| 9 | 5-NO ₂ | Me | 2 | 201 | 27 | C14H20N2O4 | C.H.N | Â | 0.35 (0.19-0.66); 0.89 • 0.035; 5 |
| 10 | 5-CN | Me | 2 | 220-221 | 5 | $C_{17}H_{20}N_{2}O_{2}$ | M ⁺ | A | $0.27 (0.23 - 0.31); 0.94 \pm 0.00; 4$ |
| 11 | 5-I | Me | 2 | oil | 2 | C ₁₆ H ₂₀ INO ₂ | M+ | С | 0.30 (0.16-0.58); 0.96 • 0.01; 5 |
| 12 | 5-Et | Me | 2 | 134-136 | 11 | C _{1s} H _{2s} NO ₂ | N.ªC.H. | С | $2.78 (1.36-5.69); 0.84 \pm 0.06; 4$ |
| 13 | 6-Et | Me | 2 | 160 | ~ 5 | C ₁ H ₂ NO ₂ | C.H.N | С | >20; 0.40; 2 |
| 14 | 6-CF ₃ | Me | 2 | 176-177 | 18 | C ₁₇ H ₂₀ F ₃ NO ₂ | C.H.N | D | >20; 0.15; 2 |
| 15 | 6-CN | Me | 2 | 191 | ~8 | C ₁₇ H ₂₀ N ₂ O ₂ | C.H.N | С | >20; 0.17; 2 |
| 16 | 5-NO ₂ | Me | | 198-199 | 42 | C16H16N2O4 | C.H.N | В | 0.15 (0.35-0.75); 0.89 • 0.02; 6 |
| 17 | 5-Et | Me | | oil | 3 | C ₁ [*] H ₂ [*] NO ₂ | M ⁺ | С | $2.17(1.46-3.23); 0.93 \pm 0.01; 4$ |
| 18 | 6-CF ₃ | Me | | 143-144 | 4 | C ₁₇ H ₁₆ F ₃ NO ₂ | C.H.N | D | >20; 0.14; 2 |
| 19 | 5-NHँ₀ | Me | | 143-144 | 100 | C _{1e} H _{1e} N ₂ O ₂ | M ⁺ | Е | >20; 0.10; 2 |
| 20 | 5-CN | Me | | 22 9 -230 | 67 | $C_{17}H_{16}N_{7}O_{7}$ | C.H.N | F | $1.94 (0.77 - 4.86); 0.81 \oplus 0.09; 3$ |
| 21 | $5-NO_2$ | Н | 1 | 204-205 | 57 | $C_{13}H_{14}N_2O_4$ | M+ | н | >20, 0.40, 2 |

^aSee text and Experimental Section. ^bIC₅₀ in micromoles with 95% confidence limits; intrinsic activity \pm SEM; no. of determinations. ^cCis isomer. ^dN; found 3.85, required 4.87%.

Table II. 3-Substituted Ind-2-enes



| compd | R | m | n | mp, °C | yield, % | formula | anal. | method ^a | inhibition of spontaneous tone in guinea pig tracheal spirals ^b |
|-------|-------------------|---|---|---------|-------------|---|-------|---------------------|---|
| 26 | $5 - NO_2$ | 0 | 2 | 113-114 | 5 | C ₁₆ H ₁₈ N ₂ O ₃ | C,H,N | Α | 2.24 (0.81-6.19); 0.94 • 0.02; 5 |
| 27 | 6-CF ₃ | 0 | 2 | 100-102 | 2 | $C_{17}H_{18}F_{3}NO$ | M+ | D | 8.5; 0.89; 2 |
| 28 | 5-NO ₂ | 0 | | 159-160 | 88 | $C_{16}H_{14}N_2O_3$ | C,H,N | G | $0.84 (0.52 - 1.37); 0.95 \pm 0.01; 4$ |
| 29 | 5-CN | 0 | | 140-141 | 87 | $C_{17}H_{14}N_2O_3$ | C,H,N | G | 5.26 (3.22-8.59); 0.77 • 0.06; 3 |
| 30 | 5-CN | 1 | | 152-153 | 59 | $C_{18}H_{16}N_2O$ | C,H,N | I | >20; 0.32; 2 |
| 31 | 5-CN | 1 | 1 | 102-103 | 50 | $C_{17}H_{14}N_2O$ | C,H,N | I | 14.0 (7.62-25.9); 0.60 • 0.03; 3 |

^a See Text and Experimental Section. ^bIC₅₀ in micromoles with 95% confidence limits; intrinsic activity **a** SEM; no. of determinations.

near quantitative yields of the indanols 3a,c-g, which underwent dehydration to the corresponding indenes 4a,c-g (70-98% yield) on heating with p-toluenesulfonic acid in toluene under conditions of azeotropic distillation of water. Those indenes containing substituents which were not readily available by the direct route shown in Scheme I were made by further manipulation of either 4c or 4d by the procedures illustrated in Scheme II. Thus, reaction of 6-bromoindene 4d with sodium trifluoroacetate and copper(I) iodide in N-methylpyrrolidinone at 60 $^{\circ}C^{9}$ afforded 4h in quantitative yield. The 6-ethyl derivative 4i was prepared from 4d by reaction with ethyl magnesium bromide and Li₂CuCl₄ following the method of Kochi,¹⁰ although a similar reaction with 4c was unsuccessful. However, a modification of the method in which (Ph₂PCH₂)₂NiCl₂¹¹ replaced the lithiocuprate, furnished



^aReagents: (i) EtMgBr, Li₂CuCl₄, THF; (ii) NaO₂CCF₃, CuI, *N*-methylpyrrolidinone; (iii) EtMgBr, (Ph₂PCH₂)₂NiCl₂, Et₂O.

the 5-ethyl compound 4j in 100% yield.

Transformation of the indenes 4a,e-j into the target compounds 7-18 (Table I) was effected either by prior conversion to the corresponding epoxides 6a,e by reaction with *m*-chloroperbenzoic acid, or more usually via the bromohydrins 5f-j, which were prepared by reaction with NBS in aqueous DMSO. In general the epoxides were

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⁽¹⁰⁾ Tamura, M.; Kochi, J. Synthesis 1971, 303.

⁽¹¹⁾ Tamao, K.; Sumitani, K.; Kumada, M. J. Am. Chem. Soc. 1972, 94, 4374.

Scheme III^a



^aReagents: (i) NaN₃, aqueous dioxane; (ii) NaBH₄, MeOH-THF, heat; (iii) Cl(CH₂)₃COCl, pyridine; (iv) K_2CO_3 , KI, DMF, heat.

reacted with the requisite amide anion (from KOBu^t) in the amide as solvent at 25-40 °C (method A) or in DMSO at room temperature (method B). The reason for the formation of the cis compound 8, which was isolated in the same yield as the expected trans compound 7, is unclear, but it presumably arises by epimerization of 7 under the reaction conditions. Epimerized products were not, however, isolated from any of the other epoxide opening reactions. The bromohydrins were similarly condensed with appropriate amide anions either by reaction in Nmethylpyrrolidinone (method C) or in DMSO (method D). In the reactions leading to the formation of 9 and 14, small vields of the corresponding amidoindenes 26 and 27 (Table II) were also isolated. Similar concomitant dehydrations have been observed in the preparation of amidobenzopyranols.^{3,4} The 5-amino compound 19 was prepared in quantitative yield by catalytic reduction of the 5-nitro analogue 16 (method E). Reaction of 19 with copper(I)cyanide under Sandmeyer conditions (method F) subsequently furnished 67% of the 5-cyano analogue 20. Both the 5-nitro and 5-cyano compounds (16 and 20, respectively) were dehydrated to the corresponding amidoindenes 28 and 29, respectively, by formation of their mesylates and subsequent elimination by treatment with KOBu^t (method G) (Table II).

Synthesis of the didemethyl indanol 21 was accomplished as outlined in Scheme III. Oxidation of 6nitroind-1-ene¹² with *m*-CPBA gave 86% of the epoxide 22, which on treatment with NaN₃ in aqueous dioxane was converted into azido alcohol 23 in reasonable yield. Attempted ring opening of the epoxide 22 with amide anions according to the procedures described above led only to extensive polymerization. Reduction of 23 using NaBH₄ in THF at reflux formed the amino alcohol 24 which on acylation with 4-chlorobutyryl chloride in pyridine at room temperature gave 42% of the amide 25. Cyclization of 25 under mildly basic conditions then resulted in the formation of 57% of the required amidoindanol 21 (method H).

The homologous amidoindenes 30 and 31 (Scheme IV) were not available by the routes described above but were prepared according to the procedure described in Scheme IV. Aminoindanone 2b was first converted into the exocyclic alkene 32 in 92% yield by reaction with (triphenylphosphonio)methanide in THF and then further modified to the cyano compound 33 by Sandmeyer reacScheme IV^a



^aReagents: (i) Ph₃P=CH₂, THF; (ii) HNO₂, CuCN, KCN; (iii) TFA, DCM; (iv) NBS, AIBN, CCl₄; (v) pyridone or pyrrolidinone, KOBu^t.

Scheme V



tion. Isomerization to the endocyclic alkene 34 was effected in 89% yield on treatment with trifluoroacetic acid at ambient temperature and this was subsequently halogenated with NBS to give 62% of the bromomethyl derivative 35. Further reaction of 35 with pyrrolidinone or pyridone anions (generated in THF with KOBu^t) then afforded the amides 30 and 31, respectively, in moderate yields (method I, Table II).

Finally the 5'-methyl derivatives 36 and 37 (Scheme V, Table III) were prepared according to method B by reaction of the 5-nitro epoxide 6a with (R)-5'-methyl- and (S)-5'-methylpyrrolidinone anion, respectively. In these instances the reaction afforded a 3:4 mixture of diastereoisomers, together with small quantities of the corresponding indenes 38 and 39. While the stereochemistry of the individual isomers, 36a and 36b isolated from the separation of 36, is not proven, the marked potency difference between them suggests that 36a has the ring stereochemistry 2R, 3R, since this is the stereochemistry which confers greater potency in the case of cromakalim.

Results and Discussion

There are now a wide diversity of structural entities which have been claimed to enhance the outward conductance of potassium ions in smooth muscle cells,¹³ and such compounds are generically termed potassium channel

⁽¹³⁾ Edwards, G.; Weston, A. H. Current Cardiovascular Patents, 1989, 1, 1810.

| | | $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | | | | |
|------------|---|--|-----------------------|---|-------------------------|-------------------------|---|--|
| compd | 5′,2,3 stereochemistry | mp, °C | yield, % | formula | anal. | $[\alpha^{25}D]_{EtOH}$ | inhibition of spontaneous tone in guinea pig tracheal spirals ^a | |
| 36 | $\left\{ \begin{array}{c} R,R,R\\ R,S,S \end{array} \right\}$ | 189–192 | 31 ^{b,c} | C ₁₆ H ₂₀ N ₂ O ₄ | M+ | | 0.26 (0.07-0.96); 0.99 • 0.01; 4 | |
| 36a 36b | R,2R,3R ^d R,2S,3S ^d | 237–238 210–211 | - - | $\substack{ C_{16}H_{20}N_2O_4\\ C_{16}H_{20}N_2O_4 }$ | C,H,N C,H,N | -20.5 -100.2 | $\begin{array}{c} 0.34 \ (0.11 - 1.09); \ 0.89 \ \pm \ 0.07; \ 4 \\ 3.90 \ (1.48 - 10.29); \ 0.90 \ \oplus \ 0.03; \ 4 \end{array}$ | |
| 37 | $\left. \begin{array}{c} S,R,R\\ S,S,S \end{array} \right\}$ | 187–191 | 21¢ | $C_{16}H_{20}N_2O_4$ | M+ | - | >20; 0.30; 2 | |
| 38 39 | R S | 138–139 oil | 17 10 ⁶ | $\substack{ C_{16}H_{18}N_2O_3\\ C_{16}H_{18}N_2O_3 }$ | C,H,N M ⁺ | -180.8 | 2.42 (0.55-10.54); 0.84 • 0.06; 4 e | |

 a IC₅₀ in micromoles with 95% confidence limits; intrinsic activity ±SEM; no. of determinators. b Yield on basis of recovered starting material. c 3:4 ratio of diastereoisomers determined by ¹H NMR. d Stereochemistry not proven; see text. e Insufficient material for evaluation.

activators or openers.² Although there have been several publications on SARs for antihypertensive activity, arising from their ability to relax vascular smooth muscle.^{3,14,15} little SAR data on their effects on the smooth muscle of airways has been published.⁴ As part of a program designed to optimize the bronchodilator activity of cromakalim, we have reported the effects of aromatic substitution on smooth muscle relaxant activity and also explored the effects of selected modifications of the amide function at C-4.4 As an extention to these investigations, we carried out some molecular modeling studies on the 6-nitro analogue of cromakalim and the nitroindanol 7, since from previous work this substituent gave compounds of similar potency to cromakalim itself³ yet offered facile entry into a range of other analogues. These studies showed that key atoms in these two molecules occupied similar spatial positions, suggesting that indanols might show activity similar to that of benzopyranols (Figure 1).

From those indanols synthesized (Table I), it is evident that activity is retained in the series and that the 3piperidinonyl compounds having nitro cyano, and iodo substituents at C-5 (9, 10, and 11, respectively) elicit greatest potency as relaxants of spontaneous tone in isolated guinea pig trachealis. As expected,^{4,14} high potency was also retained in the 5-nitro-3-pyridonyl derivative 16, but was lower than anticipated in the 5-cyano analogue 20. Potency was also reduced in the 5-ethyl derivatives 12 and 17, and in the 5-nitropyrrolidinone 7. The didemethyl homologue and cis isomer of 7 (21 and 8, respectively) and the 5-amino compound 19 were of relatively low potency. In contrast to earlier observations on the dihydrobenzopyranols,⁴ where some substituents at C-7 conferred activity, those compounds substituted at C-6 (13–15, 18) showed little activity at 20 μ M concentrations.

In the 5-substituted compounds there was a tendency for a reduction in potency on dehydration (cf. 9, 26; 16, 28; and 20, 29; Tables I and II) which was most marked with the 5-nitropiperidone 26. The one C-6 substituted compound 27, on the other hand, showed enhanced potency relative to the indanol 15.

Prompted by the observation that substitution of the pyrrolidinone moiety with a 5'-methyl group could provide potent compounds, and that this activity was exclusive to



Figure 1. Molecular overlap of compound 7 and the energy minimized form of the 6-nitro analogue of cromakalim. The fitted structure of 7 falls within 2 kcal of the energy minimized conformation as determined by the AMPAC program using the AM 1 Hamiltonian. (Stewart, J. J. P. Q.C.P.E. Bull. 1986, 6, 24a.)

the (R)-5' enantiomer,¹⁶ the 5'-methyl (R and S) analogues of 8 were prepared. Evaluation of the mixed diastereoisomers 36 and 37 (Table III) revealed that activity in this series also resided only in the (R)-5' isomer 36, and separation of the two diastereoisomers 36a and 36b from 36 indicated that activity was enhanced in 36a relative to 36b. Since it is known that the activity of cromakalim is dominant in the 3S,4R enantiomer, we have inferred that the absolute stereochemistry of 36a is 2R,3R and that of 36b is 2S,3S. It is of interest that the (R)-5'-methylindene 38, in which chirality at C-2 and C-3 is destroyed, also elicits potent airways smooth muscle relaxant activity in vitro.

Since cromakalim has been shown to elicit potent activity as a bronchodilator in vivo,⁵ we have evaluated the 5-nitro compound 16 for its ability to protect guinea pigs against histamine-induced dyspnoea. When given orally at 5 mg/kg at various times prior to challenge (Figure 2)

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⁽¹⁵⁾ Burrell, G.; Cassidy, F.; Evans, J. M.; Lightflower, D.; Stemp, G. J. Med. Chem. 1990, 33, 3023.

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Figure 2. Time course for inhibition of histamine-induced dyspnoea by compound 16 administered at 5 mg/kg po prior to challenge. Figures in parentheses represent number of animals protected over number tested. *p < 0.05.

16 showed significant protection from dyspnoea at times between 15 and 60 min post dosing, with the maximum effect occurring within 30-45 min. In a separate doseresponse experiment, the dose required to protect 50% of the animals challenged 30 min afterward was found to lie between 1.25 and 2.5 mg/kg. These results demonstrate a similar potency to that previously found for cromakalim⁵ but that 16 has a marginally reduced duration of effect.

Since the indanols reported here are structurally distinct from previously reported potassium channel activators, we have verified the mechanism of action of a representative member of the series by potassium efflux and potassium channel blocker studies. Thus, in a similar manner to that of cromakalim, 17 compound 16 (10 $\mu M)$ caused a significant stimulation of ^{42/43}K⁺ efflux from guinea pig isolated trachealis (Figure 3), with the peak efflux response being 185 \pm 10% of basal levels. Compound 16 was also shown to markedly enhance the efflux of 42/43K⁺ from guinea pig isolated portal vein. In this instance the peak rate enhancement was $338 \pm 6\%$ of basal levels.¹⁸ That potassium channel activation accounted for a substantial proportion of the smooth muscle relaxant activity of 16 was confirmed from studies using the selective potassium channel blocker BRL 31660.¹⁹ Prior incubation of guinea pig trachealis with BRL 31660 (10 μ M), a concentration which had no effect on spontaneous tone, caused a marked shift to the right of the concentration-response curve to 16 such that an IC_{50} value was not achieved even when concentrations of $20 \ \mu M$ were added to the organ bath. Comparison of these results with the inhibition of cromakalim by BRL 31660 previously reported¹⁹ supports the contention that indanols of the type described herein owe at least part of their relaxant activity to the enhancement of K⁺ conductance in smooth muscle cells.

Experimental Section

Melting points were determined with use of a Buchi apparatus and are recorded uncorrected. The structures of all compounds were consistent with their IR and ¹H NMR spectra, which were determined with a Perkin-Elmer 298 spectrophotometer and a Varian EM 390 (90 MHz) or JEOL 270 GMX (270 MHz) spectrometer, respectively. Mass spectra were recorded with a VG-Micromass 70-70F spectrometer by using electron impact techniques. Where represented by elemental symbols, the analyses of these elements fall within $\pm 0.4\%$ of the calculated values. All organic extracts were dried over MgSO₄ and samples were chromatographed on silica in all instances.

1,1-Dimethylindan-3-ols 3a,c-g. General Procedure. Potassium borohydride (1.08 g, 20 mmol) was added portionwise to a stirred solution of the indanone (2) (20 mmol) in MeOH (60 mL), and the mixture was stirred for a further 1 h at ambient temperature. The solution was then concentrated under vacuum, and the residue was partitioned between ethyl acetate and water. Evaporation of the organic phase afforded the indanols 3 (95-100%) which were isolated by recrystallization or chromatography and generally used without further purification.

1,1-Dimethylind-2-enes 4a,c-g. General Procedure. A solution of the indanol 3a,c-g (10 mmol) in toluene (60 mL) was heated at reflux under a Dean-Stark head in the presence of *p*-toluenesulfonic acid (150 mg) until no further water was collected (16 h). The solution was allowed to cool, washed with 2 M aqueous NaOH, and concentrated to yield crude indene. Chromatography or recrystallization as appropriate then yielded 4a,c-g (70-98%) of sufficient purity for the next stage.

1,1-Dimethyl-6-(trifluoromethyl)ind-2-ene (4h). Copper(I) iodide (4.58 g, 24 mmol) and CF₃CO₂Na (3.26 g, 24 mmol) were added to a solution of the 6-bromoindene 4d (1.34 g, 6 mmol) in N-methylpyrrolidinone (60 mL), and the mixture was stirred under N₂ at 160 °C for 6 h. After cooling, water and Et₂O were added and the mixture was filtered through Celite. Separation of the phases and evaporation of the dried organic layer gave 4h (1.27 g, 100%) as an oil; ¹H NMR (CDCl₃) δ 1.32 (6 H, s, CH₃) δ .53 (1 H, d, J = 6 Hz, C-2H), δ .68 (1 H, d, J = 6 Hz, C-3H), 7.38 (1 H, d, J = 9 Hz, C-4H), 7.55 (1 H, br d, J = 9 Hz, C-5H), 7.6 (1 H, br s, C-7H).

1,1-Dimethyl-6-ethylind-2-ene (4i). Dry Mg (0.225 g, 9.38 mmol) was added to a solution of the 6-bromoindene 4d (2.00 g, 9 mmol) in dry THF (50 mL) under N₂, and the mixture was stirred in the presence of a catalytic amount of I₂ until Grignard formation was complete. Ethyl bromide (1.65 g, 15 mmol) followed by a solution of dry LiCl (850 mg, 20 mmol) and copper(II) chloride (1.35 g, 10 mmol) in THF (5 mL) were added, and the mixture was stirred at ambient temperature overnight. Workup with aqueous ammonium chloride gave the indene 4i (735 mg, 48%) contaminated with a small quantity of 1,1-dimethylind-2-ene.

1,1-Dimethyl-5-ethylind-2-ene (4j). To a stirred solution of the 5-bromoindene 4c (2.00 g, 9 mmol) in anhydrous Et_2O (20 mL) under N₂ was added bis(diphenylphosphino)ethanenickel(II) chloride (47 mg, 0.09 mmol) at room temperature. A solution of ethyl magnesium bromide (3.5 mL of a 3 M solution in Et_2O , 10.5 mmol) was added dropwise with stirring over 10 min, and the mixture was heated at reflux for 16 h. After cooling, the solution was added to 2 M aqueous HCl, (10 mL) and the phases were separated. The aqueous phase was extracted with ether, and the combined ethereal solutions were dried and evaporated to afford 4j (1.54 g, 100%) as an oil: ¹H NMR (CDCl₃) δ 1.20 (9 H, m, CH₃), 2.53 (2 H, q, J = 8 Hz, CH₂), 6.27 (1 H, d, J = 5 Hz, C-2H), 6.53 (1 H, d, J = 5 Hz, C-3H), 6.93–7.27 (3 H, m, aromatic).

trans-2-Bromo-1,1-dimethylindan-3-ols 5f-j. NBS (2.90 g, 16.4 mmol) was added to a solution of the indene 4f-j (8.2 mmol) in DMSO (18 mL) and water (0.4 mL), and the mixture was stirred at room temperature overnight. Water was then added and the product was extracted into EtOAc. Evaporation and chromatography of the dried extracts furnished 5f-j (55-99%) of sufficient purity for the next stage.

1,2-Epoxy-6-nitroindan (22). *m*-Chloroperbenzoic acid (2.89 g, 13 mmol) was added to a stirred solution of 6-nitroind-1-ene (1.93 g, 12 mmol)¹² in CH₂Cl₂ (20 mL), and the mixture was stirred for an additional 2 days. The mixture was then washed sequentially with aqueous Na₂SO₃ and NaHCO₃ before drying and concentration in vacuo. Chromatography (CH₂Cl₂-hexane, 3:1) yielded 22 (1.82 g, 86%): mp (Et₂O-hexane) 95 °C; ¹H NMR (CDCl₃) δ 2.95 (1 H, dd, J = 1.5 Hz, 19 Hz, C-2H), 3.30 (1 H, d,

⁽¹⁷⁾ Foster, K. A.; Arch, J. R. S.; Morris, J. E. J.; Newson, P. N.; Taylor, S. G., to be submitted for publication.

⁽¹⁸⁾ Shaw, D. Unpublished results.

⁽¹⁹⁾ Taylor, S. G.; Foster, K. A.; Shaw, D. J.; Taylor, J. F. Br. J. Pharmacol. 1989, 98, 805P.



Figure 3. Stimulation of ${}^{42/43}$ K efflux from guinea pig isolated trachealis by 10 μ M BRL 38227 (---+---) and 10 μ M compound 16 (= Δ =). Significance is represented as follows: *p < 0.5; **p < 0.01; ***p < 0.001.

J = 19 Hz, C-1H), 4.20 (1 H, br t, J = 1.5 Hz, C-3H), 4.35 (1 H, br d, J = 3 Hz, C-3H), 7.40 (1 H, d, J = 8 Hz, C-4H), 8.20 (1 H, dd, J = 1.5 Hz, 8 Hz, C-5H), 8.4 (1 H, d, J = 1.5 Hz, C-7H). Anal. (C₉H₇NO₃) C, H, N. Compounds 6a and 6e were prepared in a similar manner.

Preparation of 3-Amino-1,1-dimethylindan-2-ols. trans-1,1-Dimethyl-5-nitro-3-(2-oxopiperidin-1-yl)indan-2-ol (9). Method A. The epoxide 6a (0.57 g, 2.8 mmol) was added to a solution of KOBu^t (0.36 g, 3.2 mmol) in 2-piperidinone (5 mL), and the stirred mixture was heated at 40 °C for 3 h. Dilute aqueous HCl (30 mL, 0.5 M) was added to the cooled mixture, and the crude product was extracted into Et₂O. The dried ethereal layer was concentrated and chromatographed (EtOAc) to afford residual 6a (50 mg) followed by 1,1-dimethyl-5-nitro-3-(2-oxopiperidin-1-yl)ind-2-ene (26) (40 mg, 5%): mp 113-114 °C, ¹H NMR (CDCl₃) δ 1.40 (6 H, s, CH₃), 2.0 (4 H, m, CH₂CH₂CH₂CH₂), 2.6 (2 H, m, CH₂CO), 3.65 (2 H, m, CH₂N), 6.3 (1 H, s, C-2H), 7.4 (1 H, d, J = 8 Hz, C-7H), 7.9 (1 H, d, J = 2 Hz, C-4H), 8.1 (1 H, dd, J = 2 Hz, 8 Hz, C-6H). Anal. (C₁₆H₁₈N₂O₃) C, H, N.

Further elution then furnished 9 (0.23 g, 27%): mp 201 °C; ¹H NMR (CDCl₃) δ 1.2 (3 H, s, CH₃), 1.4 (3 H, s, CH₃), 1.9 (4 H, m, CH₂CH₂CH₂CH₂), 2.6 (2 H, m, CH₂CO), 3.15 (2 H, t, J = 4.5 Hz, CH₂N), 3.5 (1 H, d, J = 7 Hz, OH), 4.1 (1 H, dd, J = 9.5 Hz, 7 Hz, C-2H), 6.15 (1 H, d, J = 9.5 Hz, C-3H), 7.3 (1 H, d, J = 8 Hz, C-7H), 7.85 (1 H, d, J = 1 Hz, C-4H), 8.15 (1 H, dd, J = 1, 8 Hz, C-6H). Anal. (C₁₆H₂₀N₂O₄) C, H, N.

trans-1,1-Dimethyl-5-nitro-3-(2-pyridon-1-yl)indan-2-ol (16). Method B. To a solution of 2-pyridone (6.53 g, 68.7 mmol) and KOBu^t (7.26 g, 64.8 mmol) in DMSO (30 mL) was added the epoxide 6a (2.83 g, 13.8 mmol), and the solution was stirred at ambient temperature for 72 h. The reaction was then quenched with 2 M HCl (50 mL) and the product extracted into EtOAc. The extracts were dried, concentrated, and chromatographed (gradient elution EtOAc-hexane (2:1) to EtOAc) to yield trans-1,1-dimethyl-5-nitroindan-2,3-diol (0.87 g, 28%) followed by 16 (1.76g, 42%): mp 198-199 °C; ¹H NMR (DMSO-d₆) δ 1.13 (3 H, s, CH₃), 1.4 (3 H, s, CH₃), 4.4 (1 H, br, C-2H), 5.75 (1 H, d, J =6 Hz, C-3H), 6.1 (1 H, br, OH), 6.3 (1 H, m, C-5'H), 6.5 (1 H, d, J = 9 Hz, C-3'H), 7.5 (2 H, m, C-4H + C-4' or C-6'H), 7.6 (2 H, m, C-7H + C-4' or C-6'H), 8.2 (1 H, dd, J = 2 Hz, 8 Hz, C-6H). Anal. (C₁₆H₁₆N₂O₄) C, H, N.

trans-1,1-Dimethyl-5-ethyl-3-(2-oxopiperidin-1-yl)indan-2-ol (12). Method C. KOBu^t (1.04 g, 9.3 mmol) and 2-pyridone (921 mg, 9.3 mmol) were added to a solution of the bromohydrin 5j (500 mg, 1.86 mmol) in N-methylpyrrolidinone (8 mL), and the mixture was stirred at room temperature under N₂ for 16 h. After dilution with 2 M HCl (50 mL) and extraction into EtOAc, the organic phase was evaporated and chromatographed (CHCl₃) to give 12 (60 mg, 11%) as a white crystalline solid, mp 134-136 °C. Anal. (C₁₈H₂₅NO₂) C, H.

trans-1,1-Dimethyl-3-(2-oxopiperidin-1-yl)-6-(trifluoromethyl)indan-2-ol (14). Method D. KOBu^t (0.24 g, 2.14 mmol) was added to a solution of the bromohydrin 5h (0.33 g, 1.07 mmol) in DMSO (5 mL) and, after stirring for 15 min under N₂, 2piperidone (0.53 g, 5.35 mmol) and additional KOBu^t (0.60 g, 5.35 mmol) were introduced. After 6 h the suspension was quenched as in method C and the product chromatographed (CHCl₃ to EtOAc) to provide 1,1-dimethyl-3-(2-oxopiperidin-1-yl)-6-(trifluoromethyl)ind-2-ene, 27 (8 mg, 2%) followed by compound 14 (65 mg, 18%), mp 176-177 °C. Anal. ($C_{17}H_{20}F_3NO_2$) C, H, N.

trans-5-Amino-1,1-dimethyl-3-(2-pyridon-1-yl)indan-2-ol (19). Method E. A solution of 16 (1.02 g, 3.4 mmol) in MeOH (50 mL) was hydrogenated over 10% palladinized charcoal (0.21 g) at atmospheric pressure until 3 equiv of H₂ were absorbed. The reaction mixture was filtered and concentrated to give the amino compound 19 (0.92 g, 100%): mp 143-144 °C, MS found M⁺ 270.1368 ($C_{16}H_{18}N_2O_2$ requires 270.1364).

trans-5-Cyano-1,1-dimethyl-3-(2-pyridon-1-yl)indan-2-ol (20). Method F. A solution of 19 (0.92 g, 3.41 mmol) in EtOH (5 mL) was added to concentrated HCl (0.87 mL) in water (10 mL) at 0 °C, and a solution of NaNO₂ (0.26 g, 3.77 mmol) in water (3 mL) was added dropwise such that $T \le 5$ °C. When the addition was complete the mixture was stirred for an additional 10 min and then added to a mixture of KCN (2.07 g, 30.1 mmol) and CuCN (2.86 g, 31.6 mmol) in water (10 mL) at 90 °C at such a rate that $T \ge 70$ °C. Heating was continued for a further 20 min and the mixture was cooled. Extraction with EtOAc and chromatography of the product (EtOAc) yielded 20 (0.65 g, 67%), mp (EtOAc) 229-230 °C. Anal. (C₁₇H₁₆N₂O₂) C, H, N. 1,1-Dimethyl-5-nitro-3-(2-pyridon-1-yl)ind-2-ene (28). Method G. Methanesulfonyl chloride (0.11 mL, 1.25 mmol) was added to a solution of 16 (0.34 g, 1.13 mmol) and NEt₃ (0.17 mL, 1.25 mmol) in THF (15 mL), and the mixture was stirred overnight at ambient temperature. KOBut (0.33 g, 2.95 mmol) was then added, and the resulting solution was stirred for a further 30 min before quenching with brine and extraction of the organic material into EtOAc. The dried extracts were concentrated and chromatographed (EtOAc) to yield 28 (0.28 g, 88%) as a yellow solid, mp 159-160 °C. Anal. ($C_{16}H_{14}N_2O_3$) C, H, N.

trans-1-(4-Chlorobutyramido)-6-nitroindan-2-ol (25). To a stirred solution of the epoxide 22 (5.27 g, 29.8 mmol) in dioxane (80 mL) was added a solution of NaN₃ (2.87 g, 44.2 mmol) in water (50 mL), and the mixture was stirred at room temperature for 20 h. Extraction of the organic material into Et₂O and concentration of the extracts then afforded the azido alcohol 23 (2.96 g, 46%) as a yellow oil which was used without further purification. The crude azido alcohol 23 (2.42 g, 11 mmol) was dissolved in THF (60 mL) containing NaBH₄ (2.36 g, 62 mmol), and MeOH (10 mL) was added dropwise over 1 h to the stirred mixture at reflux. When the addition was complete, the mixture was heated under reflux for a further 3 h before being cooled and diluted with brine. Extraction of the product into EtOAc and subsequent chromatography (CHCl₃ containing 5% MeOH and 0.5% aqueous NH₃ (d = 0.880)) then provided 24 (0.93 g, 43%) as a crystalline solid: mp (EtOAc-hexane) 136-137 °C; MS found M⁺ 194.0092 $(C_9H_{10}N_2O_3 \text{ requires } 194.0091).$

To a stirred solution of 24 (0.524 g, 2.70 mmol) in pyridine (20 mL) at 0 °C was added 4-chlorobutyryl chloride (0.26 mL, 3.00 mmol), and the total was stirred for 20 h at room temperature. Aqueous 2 M HCl (150 mL) was then added and the product was extracted into EtOAc. Evaporation and chromatography (EtOAc) of the dried extracts gave 25 (0.334 g, 42%): mp 140–141 °C; ¹H NMR (CDCl₃) δ 2.25 (2 H, m, CH₂CH₂), 2.55 (2 H, m, COCH₂), 3.05 (1 H, dd, J = 8 Hz, 17 Hz, C-3H), 3.44 (1 H, dd, J = 8, 17 Hz, C-3H), 5.25 (1 H, distorted t, J = 6 Hz, C-1H), 6.1 (1 H, br s, NH), 7.4 (1 H, d, J = 8 Hz, C-4H), 8.1 (1 H, br s, C-7H), 8.2 (1 H, dd, J = 2, 8 Hz, C-5H). Anal. (C₁₃H₁₅ClN₂O₄) C, H, N.

trans-6-Nitro-1-(2-oxopyrrolidin-1-yl)indan-2-ol (21). Method H. A mixture of the acyclic amide 25 (0.256 g, 0.86 mmol), KI (0.49 g, 2.95 mmol), and K_2CO_3 (5.7 g, 41.3 mmol) in DMF (15 mL) was stirred at 50 °C for 16 h, and the cooled solution was concentrated under vacuum. Partition of the residue between EtOAc and water and chromatography (EtOAc-EtOH; 95:5) of the product isolated from the organic phase then yielded 21 (0.128 g, 57%): mp 204-205 °C dec; ¹H NMR (DMSO- d_6) & 2.0 (2 H, m, CH₂CH₂CH₂), 2.4 (2 H, M, CH₂CO), 2.8 (1 H, dd, J = 8.5 Hz, 16.5 Hz, C-3H), 3.05 (1 H, m, C-3H), 3.3 (2 H, m, NCH₂), 4.5 (1 H, distorted q, J = 7.4 Hz, C-2H), 5.0 (1 H, br s, OH), 5.3 (1 H, dd, J = 1 Hz, 8 Hz, C-5H); MS found M⁺ 262.0946 (C₁₃H₁₄N₂O₄ requires 262.0954).

3-(Bromomethyl)-5-cyano-1,1-dimethylind-2-ene (35). KOBu^t (6.04 g, 53.9 mmol) was added to a stirred solution of methyltriphenylphosphonium bromide (19.03 g, 53.3 mmol) in THF (100 mL) at -78 °C, and after 10 min a solution of the aminoindanone 2b (4.06 g, 23.2 mmol) in THF (20 mL) was added. The mixture was allowed to gradually attain ambient temperature and was stirred for an additional 72 h. Brine was then added and the product extracted into Et₂O. Evaporation and chromatography (CH₂Cl₂) of the dried extracts gave the exocyclic alkene **32** (3.85 g, 96%) as a yellow oil.

To a solution of 32 (3.24 g, 18.7 mmol) in EtOH (20 mL) at 0 °C was added concentrated HCl (4.8 mL) in water (40 mL) and a solution of NaNO₂ (1.40 g, 20.2 mmol) in water (10 mL) was added dropwise with stirring such that $T \leq 5$ °C. When the addition was complete, the mixture was stirred for an additional 15 min at 0 °C before added dropwise to a solution of KCN (5.60 g, 83.6 mmol) and CuCN (7.90 g, 84.5 mmol) in water (50 mL) at 90 °C such that $T \geq 70$ °C. Heating was continued for a further 20 min, and the cooled reaction mixture was extracted with EtOAc. The combine extracts were dried, concentrated, and chromatographed (CHCl₃-hexane, 2:1) to yield the cyanoalkene 33 (1.62 g, 47%) as an oil. Compound 33 (0.871 g, 4.75 mmol) was isomerized by dissolution in a solution of CF₃CO₂H (0.5 mL) in CH₂Cl₂ $(10\ mL)$ and stirring at room temperature for 7 h. Concentration and chromatography (CH_2Cl_2-hexane; 1:1) gave 34 (0.77 g, 89%) as an oil.

NBS (0.60 g, 3.37 mmol) and azoisobutyronitrile (10 mg) were added to a solution of **34** (0.56, 3.06 mmol) in CCl₄ (7 mL), and the stirred mixture was irradiated with a 120-W tungsten lamp for 18 h. The resulting mixture was cooled, filtered, and concentrated to give crude **35**. Chromatography (EtOAc-hexane; 1:4) afforded pure **35** (0.50 g, 62%) as an oil: ¹H NMR (CDCl₃) δ 1.3 (6 H, s, CH₃), 4.35 (2 H, d, J = 0.8 Hz, CH₂), 6.5 (1 H, br s, C-2H), 7.4 (1 H, d, J = 8 Hz, C-7 H), 7.55 (1 H, dd, J = 1.5, 8 Hz, C-6H), 7.7 (1 H, d, J = 1.5 Hz, C-4H); MS found M⁺ 261.0154 (C₁₃H₁₂Br N requires 261.0160).

5-Cyano-1,1-dimethyl-3-[(2-pyridon-1-yl)methyl]ind-2-ene (30). Method I. To a stirred solution of 2-pyridone anion (from 2-pyridone (0.067 g, 0.71 mmol) and KOBu^t (0.077 g, 0.69 mmol)) in dry THF (5 mL) was added a solution of 35 (0.160 g, 0.61 mmol) in THF (1 mL), and the mixture was stirred for 56 h at ambient temperature. Water (15 mL) was added, and the product was extracted into EtOAc. Concentration and chromatography (EtOAc-hexane; 3:1) of the dried extracts gave 30 (0.10 g, 59%), mp 152-153 °C. Anal. ($C_{18}H_{16}N_2O$) C, H, N.

Relaxation of Guinea Pig Isolated Tracheal Spirals. Guinea pig tracheal spiral strips were prepared and suspended under isometric conditions in oxygenated Krebs solution. Tension was allowed to develop spontaneously and was maintained at 2 g. Compounds were added in a cumulative fashion, and the inhibitory effects were calculated as a percentage of the relaxation induced by isoprenaline (10^{-3} M) added at the end of the experiment. The IC₅₀ value of each compound was that concentration which produced 50% of the response to isoprenaline a geometric mean of four or more determinations. The intrinsic activity (IA) for each compound was calculated as the ratio of its maximum relaxation produced by isoprenaline (10^{-3} M) and expressed as an arithmetic mean.

Bronchoconstriction in Conscious Guinea Pigs. Male guinea pigs (400-460 g) were dosed orally with the compound or the vehicle and placed in a Perspex chamber of approximately 8-L capacity. At various times subsequent to dosing, the animals were challenged for 4 min with a histamine aerosol generated over 20 s from a 5 mM solution of histamine diphosphate by using a Monaghan 675 ultrasonic nebulizer (power setting 7). The time from the introduction of the aerosol to collapse was recorded, with those animals not collapsing within the 4 min observation time being considered to be fully protected. The time to optimal activity, T_{max} , was determined from the time course experiments.

Potassium Efflux Experiments. Tracheae excised from male Dunkin-Hartley guinea pigs (300–600 g) were cleaned of adhering fat and connective tissue and opened by longitudinal section. The trachealis muscle was dissected free from the organ, divided into three segments and each segment was randomly assigned to the various treatment groups. Following a preincubation at 37 °C in 2.5 mL of Krebs solution bubbled with 95% O₂-5% CO₂, tissues were loaded with $^{42/43}$ K (37–74 MBq/L) at 37 °C in 2.5 mL of Krebs solution for 60 min. Efflux was followed by transferring tissues through a sequence of 17 washing samples at 37 °C, with a resident time in each wash of 3 min. When present, compound 16 was added to tubes 11–14. At the end of the efflux period, the tissues were blotted and the radioactivity in both tissues and washing samples was measured by γ -counting. Efflux was calculated as a rate coefficient (fractional loss of radioactivity from the tissue per minute, expressed as a percentage).

Acknowledgment. The authors thank Mrs. D. Shaw for carrying out the efflux work reported for compound 16.

Registry No. 2a, 67159-79-9; 2b, 67159-81-3; 2c, 67159-84-6; 2d, 67159-85-7; 2e, 124369-41-1; 2f, 131406-59-2; 2g, 124369-62-6; (\pm) -3a, 131406-79-6; (\pm) -3c, 131406-80-9; (\pm) -3d, 131406-81-0; (\pm) -3e, 131406-82-1; (\pm) -3f, 131406-83-2; (\pm) -3g, 131406-84-3; 4a, 124369-37-5; 4c, 124369-45-5; 4d, 124369-47-7; 4e, 124369-43-3; 4f, 131406-85-4; 4g, 124369-49-9; 4h, 124369-54-6; 4i, 124369-48-8; 4j, 124369-46-6; (\pm) -5f, 131406-86-5; (\pm) -5g, 131406-87-6; (\pm) -5h, 131406-88-7; (\pm) -5i, 131406-89-8; (\pm) -5j, 131406-90-1; (\pm) -6a, 131406-92-3; (\pm)-6e, 131406-93-4; (\pm)-7, 131406-60-5; (\pm)-8, 131406-61-6; (\pm)-9, 131406-62-7; (\pm)-10, 131406-63-8; (\pm)-11, 131406-64-9; (\pm)-12, 131406-65-0; (\pm)-13, 131406-66-1; (\pm)-14, 131406-67-2; (\pm)-15, 131406-68-3; (\pm)-16, 131406-69-4; (\pm)-17, 131406-70-7; (\pm)-18, 131406-71-8; (\pm)-19, 131406-72-9; (\pm)-20, 131406-73-0; (\pm)-21, 131406-74-1; (\pm)-22, 131406-91-2; (\pm)-23, 131406-94-5; (\pm)-24, 131406-95-6; (\pm)-25, 131406-96-7; 26, 124369-09-1; 27, 124369-21-7; 28, 124369-34-2; 29, 124369-13-7; **30**, 124369-29-5; **31**, 124369-28-4; **32**, 124369-65-9; **33**, 124369-66-0; **34**, 124369-67-1; **35**, 124369-68-2; **36a**, 131406-75-2; **36b**, 131406-76-3; (2R,3R)-**37**, 131406-77-4; (2S,3S)-**37**, 131406-78-5; **38**, 124369-31-9; **39**, 124369-32-0; CF₃CO₂N₉, 2923-18-4; Cl(CH₂)₃COCl, 4635-59-0; K, 7440-09-7; 6-nitroind-1-ene, 41734-55-8; 2-piperidone, 675-20-7; 2-pyrrolidinone, 616-45-5; 2-pyridone, 142-08-5; (R)-5-methyl-2-pyrrolidinone, 21395-93-7; (S)-5-methyl-2-pyrrolidinone, 1558-60-7.