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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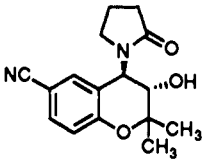
The synthesis of a novel series of smooth muscle relaxants which have been shown to act via the opening or activation of potassium channels is described. Compounds have been evaluated for their ability to inhibit spontaneous tone in guinea pig isolated trachealis and structure–activity relationships 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 μM and was found to significantly inhibit histamine-induced dyspnoea in conscious guinea pigs when given orally 30–45 min prior to challenge.

Introduction

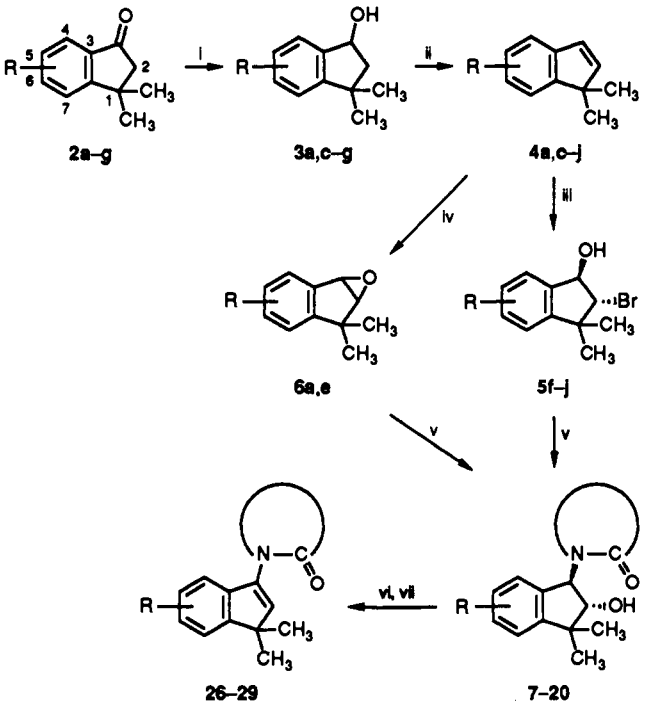
Potassium channel activators, or openers, have attracted considerable attention because of evidence for their potential value in the treatment of those disorders in which smooth muscle contraction is involved.[1] Particular applications include asthma, hypertension, and urinary incontinence, and many 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 (3*S*,4*R*) enantiomer BRL 38227 have demonstrated the ability of these compounds to prevent bronchospasm in vivo when administered either orally[5] or by inhalation.[6] Furthermore, limited studies with cromakalim 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.



1
(±)-cromakalim
BRL 38227 (3*S*,4*R*)

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

Scheme I[a]



[a] Reagents: (i) KBH_4, MeOH; (ii) *p*-TSA, PhH, reflux; (iii) NBS, H_2O, DMSO; (iv) *m*-CPBA, DCM; (v) pyrrolidinone, piperidone, or pyridone, $KOBu^t$, heat; (vi) $MeSO_2Cl$, NEt_3, THF; (vii) $KOBu^t$.

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

(1) Hamilton, T. C.; Weston, A. H. *Gen. Pharmacol.* **1989**, *20*, 1. Cook, N. S. *Trends Pharmacol. Sci.* **1988**, *9*, 21.
(2) Robertson, D. W.; Steinberg, M. I. *Ann. Rep. Med. Chem.* **1989**, *24*, 91.
(3) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194.
(4) Buckle, D. R.; Arch, J. R. S.; Fenwick, A. E.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G.; Taylor, S. G.; Tedder, J. M. *J. Med. Chem.* **1990**, *33*, 3028.
(5) Arch, J. R. S.; Buckle, D. R.; Bumstead, J.; Clarke, G. D.; Taylor, J. F.; Taylor, S. G. *Br. J. Pharmacol.* **1988**, *95*, 763.
(6) Bowring, N. E.; Taylor, J. F.; Francis, G. R.; Arch, J. R. S. *Br. J. Pharmacol.* **1989**, *98*, 805P.
(7) Williams, A. J.; Vyce, T.; Richards, D. J.; Lee, T. *Allergy Proc.* **1989**, 249.
(8) Smith, J. G.; Massicotte, M. P. *Org. Prep. Proc. Int.* **1978**, *10*, 123.

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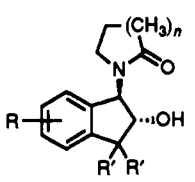
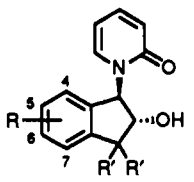
Table I. 3-Amidoindan-2-ols



7-15,21

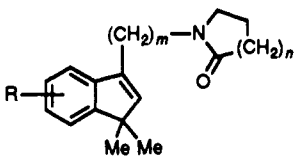


16-20

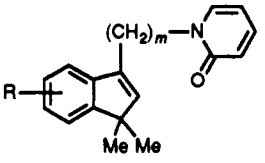
compd	R	R^1	n	mp, °C	yield, %	formula	anal.	method[a]	inhibition of spontaneous tone in guinea pig tracheal spirals[b]
cromakalim									1.1 (0.06–1.9); 0.89 ± 0.02; 7
BRL 38227									0.49 (0.36–0.67); 0.88 ± 0.02; 10
7	5-NO_2	Me	1	222–223	24	$C_{15}H_{18}N_2O_4$	C,H,N	A	2.80 (1.66–4.74); 0.88 ± 0.03; 6
8[c]	5-NO_2	Me	1	144–145	24	$C_{15}H_{18}N_2O_4$	C,H,N	A	>20; 0.26; 2
9	5-NO_2	Me	2	201	27	$C_{16}H_{20}N_2O_4$	C,H,N	A	0.35 (0.19–0.66); 0.89 ± 0.035; 5
10	5-CN	Me	2	220–221	5	$C_{17}H_{20}N_2O_2$	M^+	A	0.27 (0.23–0.31); 0.94 ± 0.00; 4
11	5-I	Me	2	oil	2	$C_{16}H_{20}INO_2$	M^+	C	0.30 (0.16–0.58); 0.96 ± 0.01; 5
12	5-Et	Me	2	134–136	11	$C_{18}H_{25}NO_2$	N,[d]C,H,	C	2.78 (1.36–5.69); 0.84 ± 0.06; 4
13	6-Et	Me	2	160	~5	$C_{18}H_{25}NO_2$	C,H,N	C	>20; 0.40; 2
14	6-CF_3	Me	2	176–177	18	$C_{17}H_{20}F_3NO_2$	C,H,N	D	>20; 0.15; 2
15	6-CN	Me	2	191	~8	$C_{17}H_{20}N_2O_2$	C,H,N	C	>20; 0.17; 2
16	5-NO_2	Me		198–199	42	$C_{16}H_{16}N_2O_4$	C,H,N	B	0.15 (0.35–0.75); 0.89 ± 0.02; 6
17	5-Et	Me		oil	3	$C_{18}H_{21}NO_2$	M^+	C	2.17 (1.46–3.23); 0.93 ± 0.01; 4
18	6-CF_3	Me		143–144	4	$C_{17}H_{16}F_3NO_2$	C,H,N	D	>20; 0.14; 2
19	5-NH_2	Me		143–144	100	$C_{16}H_{18}N_2O_2$	M^+	E	>20; 0.10; 2
20	5-CN	Me		229–230	67	$C_{17}H_{16}N_2O_2$	C,H,N	F	1.94 (0.77–4.86); 0.81 ± 0.09; 3
21	5-NO_2	H	1	204–205	57	$C_{13}H_{14}N_2O_4$	M^+	H	>20, 0.40, 2

[a] See text and Experimental Section. [b] IC_{50} in micromoles with 95% confidence limits; intrinsic activity ± SEM; no. of determinations. [c] Cis isomer. [d] N; found 3.85, required 4.87%.

Table II. 3-Substituted Ind-2-enes



26-27,31



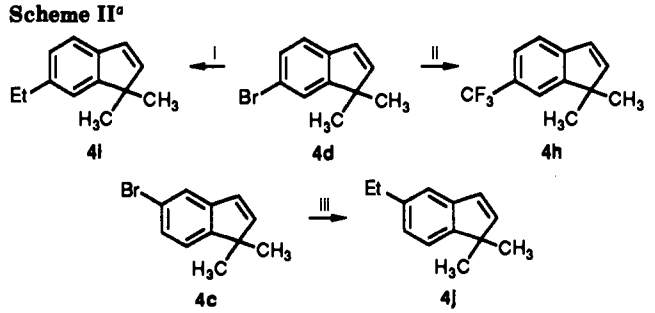
28-30

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	$C_{16}H_{18}N_2O_3$	C,H,N	A	2.24 (0.81–6.19); 0.94 ± 0.02; 5
27	6-CF_3	0	2	100–102	2	$C_{17}H_{16}F_3NO$	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 ± 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. [b] IC_{50} in micromoles with 95% confidence limits; intrinsic activity ± 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 °C[9] afforded **4h** in quantitative yield. The 6-ethyl derivative **4i** was prepared from **4d** by reaction with ethyl magnesium bromide and Li_2CuCl_4 following the method of Kochi,[10] although a similar reaction with **4c** was unsuccessful. However, a modification of the method in which $(Ph_2PCH_2)_2NiCl_2$[11] replaced the lithiocuprate, furnished

Scheme II[a]



[a] Reagents: (i) EtMgBr, Li_2CuCl_4, THF; (ii) NaO_2CCF_3, CuI, *N*-methylpyrrolidinone; (iii) EtMgBr, $(Ph_2PCH_2)_2NiCl_2$, Et_2O.

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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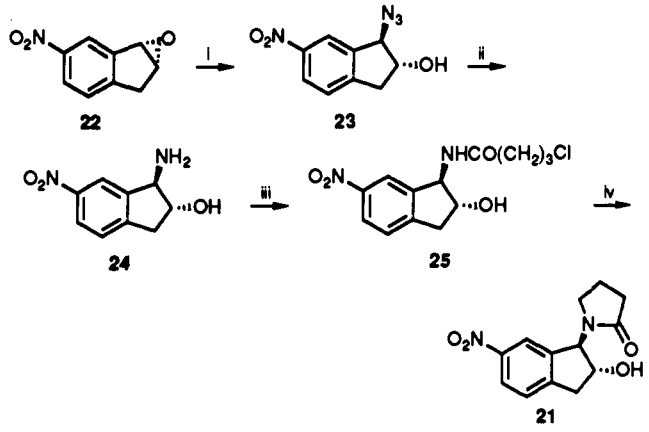
(10) Tamura, M.; Kochi, J. *Synthesis* 1971, 303.
(11) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* 1972, *94*, 4374.

Scheme III[a]



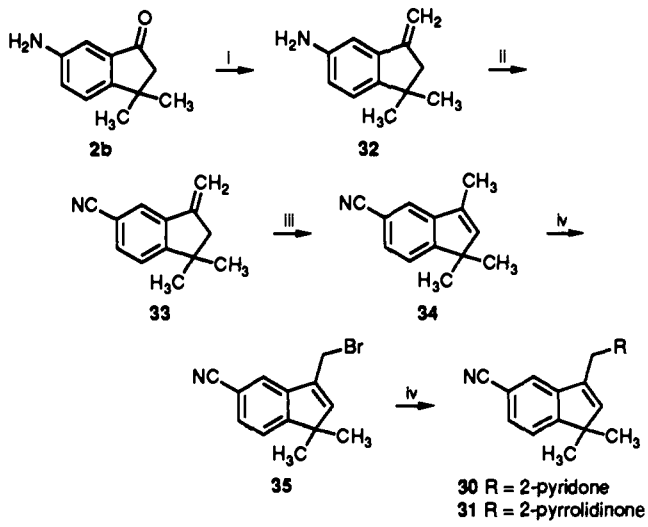
[a] Reagents: (i) NaN_3, aqueous dioxane; (ii) $NaBH_4$, MeOH–THF, heat; (iii) $Cl(CH_2)_3COCl$, pyridine; (iv) K_2CO_3, KI, DMF, heat.

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 *N*-methylpyrrolidinone (method C) or in DMSO (method D). In the reactions leading to the formation of **9** and **14**, small yields 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 6-nitroind-1-ene[12] with *m*-CPBA gave 86% of the epoxide **22**, which on treatment with NaN_3 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 $NaBH_4$ 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).

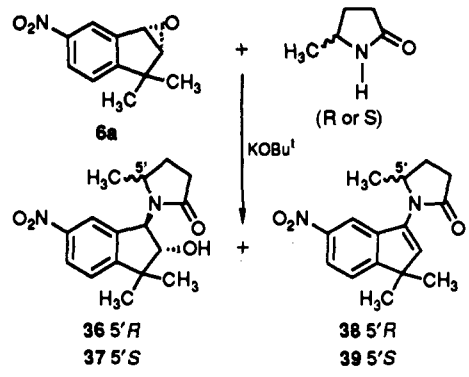
The homologous amidoindenes **30** and **31** (Scheme IV) were not available by the routes described above but were prepared according to the procedure described in Scheme IV. Aminoindanone **2b** was first converted into the exocyclic alkene **32** in 92% yield by reaction with (triphenylphosphonio)methanide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

Scheme IV[a]



[a] Reagents: (i) $Ph_3P{=}CH_2$, THF; (ii) HNO_2, CuCN, KCN; (iii) TFA, DCM; (iv) NBS, AIBN, CCl_4; (v) pyridone or pyrrolidinone, $KOBu^t$.

Scheme V



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 2*R*,3*R*, since this is the stereochemistry which confers greater potency in the case of cromakalim.

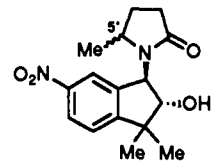
Results and Discussion

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

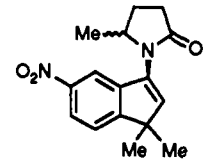
(12) Miller, R. B.; Frinke, J. M. *J. Org. Chem.* **1980**, *45*, 5312.

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

Table III. 5'-Methyl-5-nitro-3-(pyrrolidon-1-yl)indanols and -indenes



36,37



38,39

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	R,R,R / R,S,S	189–192	31[b,c]	$C_{16}H_{20}N_2O_4$	M+	-	0.26 (0.07–0.96); 0.99 ± 0.01; 4
36a	R,2R,3R[d]	237–238	-	$C_{16}H_{20}N_2O_4$	C,H,N	-20.5	0.34 (0.11–1.09); 0.89 ± 0.07; 4
36b	R,2S,3S[d]	210–211	-	$C_{16}H_{20}N_2O_4$	C,H,N	-100.2	3.90 (1.48–10.29); 0.90 ± 0.03; 4
37	S,R,R / S,S,S	187–191	21[c]	$C_{16}H_{20}N_2O_4$	M+	-	>20; 0.30; 2
38	R	138–139	17	$C_{16}H_{18}N_2O_3$	C,H,N	-180.8	2.42 (0.55–10.54); 0.84 ± 0.06; 4
39	S	oil	10[b]	$C_{16}H_{18}N_2O_3$	M+	-	e

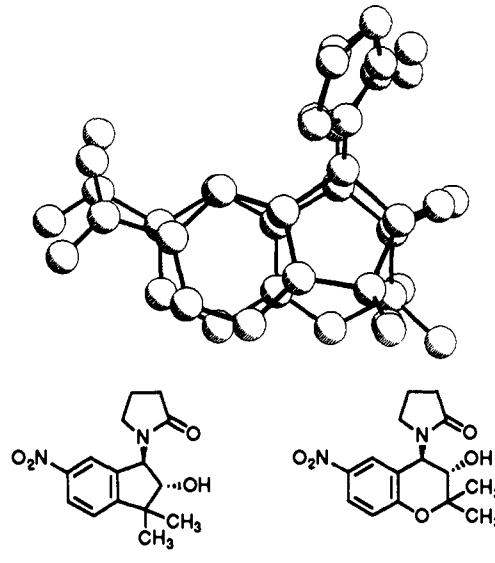
[a] IC_{50} in micromoles with 95% confidence limits; intrinsic activity ±SEM; no. of determinators. [b] Yield on basis of recovered starting material. [c] 3:4 ratio of diastereoisomers determined by ^1H NMR. [d] Stereochemistry not proven; see text. [e] Insufficient material for evaluation.

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 itself[3] 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 3-piperidinonyl 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 μM 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



7

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 3*S*,4*R* enantiomer, we have inferred that the absolute stereochemistry of **36a** is 2*R*,3*R* and that of **36b** is 2*S*,3*S*. 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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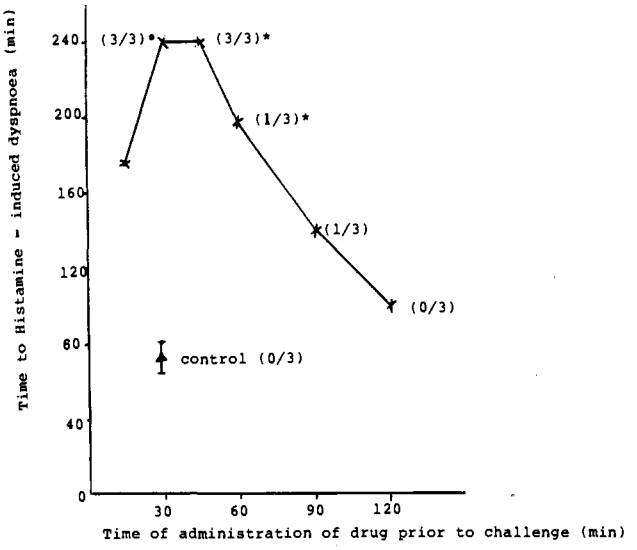

Figure 2. Time course for inhibition of histamine-induced dyspnoea by compound **16** administered at 5 mg/kg po prior to challenge. Figures in parentheses represent number of animals protected over number tested. $*p < 0.05$.

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 dose–response 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 cromakalim[5] 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 μM) caused a significant stimulation of $^{42/43}K^+$ efflux from guinea pig isolated trachealis (Figure 3), with the peak efflux response being 185 ± 10% of basal levels. Compound **16** was also shown to markedly enhance the efflux of $^{42/43}K^+$ from guinea pig isolated portal vein. In this instance the peak rate enhancement was 338 ± 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 μM), 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 μM were added to the organ bath. Comparison of these results with the inhibition of cromakalim by BRL 31660 previously reported[19] 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 ±0.4% of the calculated values. All organic extracts were dried over $MgSO_4$ 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 CF_3CO_2Na (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 N_2 at 160 °C for 6 h. After cooling, water and Et_2O 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 ($CDCl_3$) δ 1.32 (6 H, s, CH_3) 6.53 (1 H, d, J = 6 Hz, C-2H), 6.68 (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 N_2, and the mixture was stirred in the presence of a catalytic amount of I_2 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 N_2 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 ($CDCl_3$) δ 1.20 (9 H, m, CH_3), 2.53 (2 H, q, J = 8 Hz, CH_2), 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 CH_2Cl_2 (20 mL), and the mixture was stirred for an additional 2 days. The mixture was then washed sequentially with aqueous Na_2SO_3 and $NaHCO_3$ before drying and concentration in vacuo. Chromatography (CH_2Cl_2–hexane, 3:1) yielded **22** (1.82 g, 86%): mp (Et_2O-hexane) 95 °C; ^1H NMR ($CDCl_3$) δ 2.95 (1 H, dd, J = 1.5 Hz, 19 Hz, C-2H), 3.30 (1 H, d,

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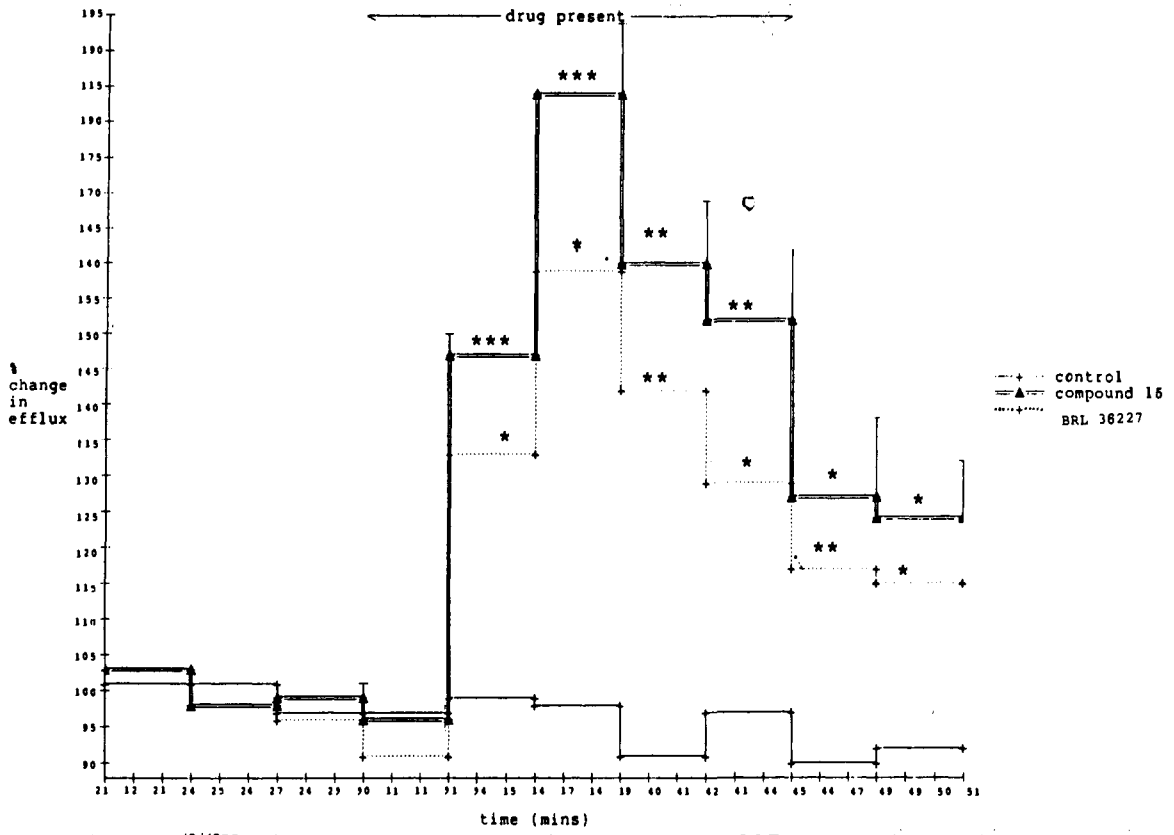

Figure 3. Stimulation of $^{42/43}K$ efflux from guinea pig isolated trachealis by 10 μM BRL 38227 (---+---) and 10 μM compound **16** (=▲=). Significance is represented as follows: *$p < 0.5$; **$p < 0.01$; ***$p < 0.001$.

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. ($C_9H_7NO_3$) 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 Et_2O. 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 ($CDCl_3$) δ 1.40 (6 H, s, CH_3), 2.0 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.6 (2 H, m, CH_2CO), 3.65 (2 H, m, CH_2N), 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. ($C_{16}H_{18}N_2O_3$) C, H, N.

Further elution then furnished **9** (0.23 g, 27%): mp 201 °C; ^1H NMR ($CDCl_3$) δ 1.2 (3 H, s, CH_3), 1.4 (3 H, s, CH_3), 1.9 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.6 (2 H, m, CH_2CO), 3.15 (2 H, t, J = 4.5 Hz, CH_2N), 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. ($C_{16}H_{20}N_2O_4$) 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-d_6) δ 1.13 (3 H, s, CH_3), 1.4 (3 H, s, CH_3), 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. ($C_{16}H_{16}N_2O_4$) 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 N_2 for 16 h. After dilution with 2 M HCl (50 mL) and extraction into EtOAc, the organic phase was evaporated and chromatographed ($CHCl_3$) to give **12** (60 mg, 11%) as a white crystalline solid, mp 134–136 °C. Anal. ($C_{18}H_{25}NO_2$) 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 N_2, 2-piperidone (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 ($CHCl_3$ 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 H_2 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 $NaNO_2$ (0.26 g, 3.77 mmol) in water (3 mL) was added dropwise such that $T \leq 5$ °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 $T \geq 70$ °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. ($C_{17}H_{16}N_2O_2$) 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 NEt_3 (0.17 mL, 1.25 mmol) in THF (15 mL), and the mixture was stirred overnight at ambient temperature. $KOBu^t$ (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 NaN_3 (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 Et_2O 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 $NaBH_4$ (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 ($CHCl_3$ containing 5% MeOH and 0.5% aqueous NH_3 (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 ($C_9H_{10}N_2O_3$ 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 ($CDCl_3$) δ 2.25 (2 H, m, $CH_2CH_2CH_2$), 2.55 (2 H, m, $COCH_2$), 3.05 (1 H, dd, J = 8 Hz, 17 Hz, C-3H), 3.44 (1 H, dd, J = 8, 17 Hz, C-3H), 3.7 (2 H, t, J = 6 Hz, CH_2Cl), 4.5 (2 H, m, C-2H + OH), 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. ($C_{13}H_{15}ClN_2O_4$) 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) δ 2.0 (2 H, m, $CH_2CH_2CH_2$), 2.4 (2 H, M, CH_2CO), 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, NCH_2), 4.5 (1 H, distorted q, J = 7.4 Hz, C-2H), 5.0 (1 H, br s, OH), 5.3 (1 H, d, J = 7.4 Hz, C-1H), 7.5 (1 H, d, J = 8 Hz, C-4H), 7.8 (1 H, br s, C-7H), 8.1 (1 H, dd, J = 1 Hz, 8 Hz, C-5H); MS found M^+ 262.0946 ($C_{13}H_{14}N_2O_4$ 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 Et_2O. Evaporation and chromatography (CH_2Cl_2) 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 $NaNO_2$ (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 ($CHCl_3$–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 CF_3CO_2H (0.5 mL) in CH_2Cl_2 (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 CCl_4 (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 ($CDCl_3$) δ 1.3 (6 H, s, CH_3), 4.35 (2 H, d, J = 0.8 Hz, CH_2), 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 ($C_{13}H_{12}BrN$ 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 IC_{50} value of each compound was that concentration which produced 50% of the response to isoprenaline as measured from the dose–response curve and was generally a geometric mean of four or more determinations. The intrinsic activity (IA) for each compound was calculated as the ratio of its maximum relaxant activity at concentrations up to 20 μM over the 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% O_2–5% CO_2, 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).

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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; (±)-**3a**, 131406-79-6; (±)-**3c**, 131406-80-9; (±)-**3d**, 131406-81-0; (±)-**3e**, 131406-82-1; (±)-**3f**, 131406-83-2; (±)-**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; (±)-**5f**, 131406-86-5; (±)-**5g**, 131406-87-6; (±)-**5h**, 131406-88-7; (±)-**5i**, 131406-89-8; (±)-**5j**, 131406-90-1; (±)-**6a**,

131406-92-3; (±)-**6e**, 131406-93-4; (±)-**7**, 131406-60-5; (±)-**8**, 131406-61-6; (±)-**9**, 131406-62-7; (±)-**10**, 131406-63-8; (±)-**11**, 131406-64-9; (±)-**12**, 131406-65-0; (±)-**13**, 131406-66-1; (±)-**14**, 131406-67-2; (±)-**15**, 131406-68-3; (±)-**16**, 131406-69-4; (±)-**17**, 131406-70-7; (±)-**18**, 131406-71-8; (±)-**19**, 131406-72-9; (±)-**20**, 131406-73-0; (±)-**21**, 131406-74-1; (±)-**22**, 131406-91-2; (±)-**23**, 131406-94-5; (±)-**24**, 131406-95-6; (±)-**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; (2*R*,3*R*)-**37**, 131406-77-4; (2*S*,3*S*)-**37**, 131406-78-5; **38**, 124369-31-9; **39**, 124369-32-0; $CF_3CO_2N_9$, 2923-18-4; $Cl(CH_2)_3COCl$, 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.