included the peak intravesical bladder pressure (P_{ves}) defined as the difference between the maximum pressure and the threshold pressure. Threshold pressure is defined as the intravesical pressure just before the elicited contraction. Each animal served as its own control. Drug potencies were assessed by iv (femoral) infusions of increasing drug doses given during the rest phase of a series of CMGs. The resultant reduction in peak contraction was expressed relative to control peak P_{ves} values obtained in absence of drug. ID_{50} and ID_{80} values were defined as the contraction of drug that inhibited peak P_{ves} by 50% and 80%, respectively, and were calculated by using probit analysis.

Acknowledgment. We acknowledge Greg A. Erickson, Valerie C. Lowe, and Jan S. Peterson for valuable technical assistance. We are grateful to Carol L. Friend for the preparation of the manuscript.

3-Methyl-2*H*-1-benzopyran Potassium Channel Activators

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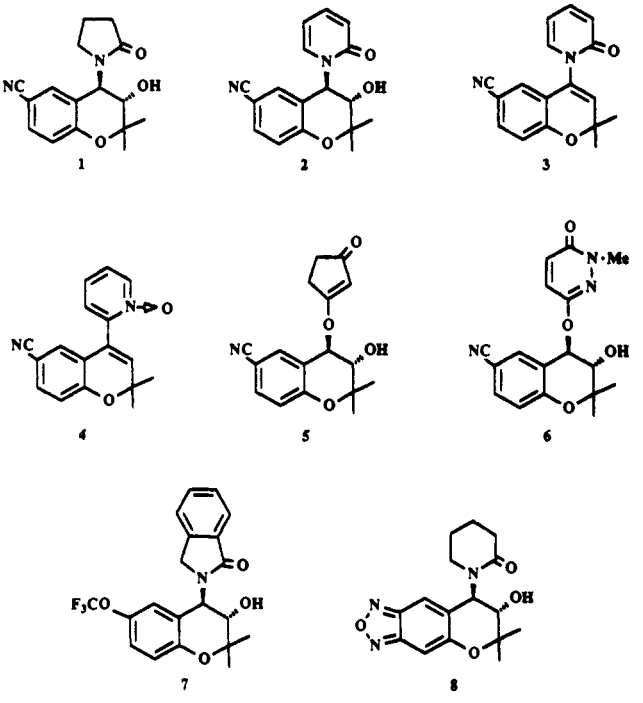
By aldol condensation of 4-chromanones with paraformaldehyde, 3-alkylenechromanones **10** were obtained which gave 3-alkylchromenes following reduction and dehydration. Subsequent 3-chloroperbenzoic acid oxidation produced the versatile epoxide intermediates **15**, from which 3,4-epoxy-3,4-dihydro-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (**15a**) was resolved into its enantiomers by entrainment. In addition to the methyl group, the benzyl, alkyloxymethyl, and 2-nitroethyl residues could be introduced in the 3-position. Treatment of **15a** with 2-pyridone simultaneously gave N- and O-substituted products **19a** and **20**. **19a** easily gave 4-(1,2-dihydro-2-oxo-1-pyridyl)chromene **21** by treatment with base. The corresponding pyrrolidinone compounds **26** and **27** were obtained by a slightly modified procedure. Reaction with 2,4-dihydroxypyridine or 3,6-pyridazinediol resulted in the exclusive formation of 4-(heterocyclyloxy)chromanols (**31** and **32**). Treatment of **15a** with 3-amino-6-pyridazinol gave 4-(3-amino-1,6-dihydro-6-oxo-1-pyridazinyl)chromanol derivative **34** lacking an NH bridge. This could be established after methylation of the ring-nitrogen atom (→**35**). Trans-configurated 3-methyl-4-pyridone compound **36** was obtained by addition of methyllithium to chromene **3**. Hyperpolarizing and antispasmodic or relaxing effects of the compounds were determined in organ bath studies using pig coronary arteries precontracted with acetylcholine or rabbit main pulmonary arteries precontracted with noradrenaline. In the 3-methyl series the classical pyridone and pyrrolidinone structures (**9**, **21**, **26**, **27**) were only weakly active or inactive, but the corresponding 4-(heterocyclyloxy) and 4-(heterocyclylamino) derivatives (**31**, **32**, **35**) were even more potent than the demethyl analogues. In conformation/activity investigations it was found that the activity of the 4-substituted benzopyran derivatives seems to be dependent on the relative orientation of their ring systems.

K^+ channels play an important and complex role in the basic electrical and mechanical functions of a wide variety of tissues, including smooth muscle, cardiac muscle, and glands. Recent publications[1,2] have indicated that various compounds which increase the open probability of specific potassium channels are relaxants of a number of smooth muscle types. The first therapeutic drug shown to possess this mechanism of action was the coronary vasodilator nicorandil. Other substances that open adenosine triphosphate sensitive potassium channels are the vasodilators pinacidil, minoxidil sulfate, diazoxide, and RP 52 891. None of these substances is structurally related to any of the others.

In addition, the 2*H*-1-benzopyrans should be considered. Although up to now no product based on this structural class has been brought to the market, it is already clear that these are of immense importance within the potassium channel activators. A number of compounds are currently being developed by several pharmaceutical companies, and clinical trials are being carried out in different therapeutic areas. Development has proceeded furthest with cromakalim and its enantiomer lemakalim (**1**; Chart I). Structure/activity investigations[3,4] have shown that the

Chart I. The Chroman-Type Potassium Channel Openers



structure of **1** can be varied in many ways. The substitution of the 4-(2-oxo-1-pyrrolidinyl) group with other heterocyclic groups was successful. Substitution with an α-pyridone, for example, led to EMD 56 431 (**2**).[5] In the

(1) Robertson, D. W.; Steinberg, M. I. Potassium Channel Modulators: Scientific Applications and Therapeutic Promise. *J. Med. Chem.* **1990**, *33*, 1529–1541.

(2) Steinberg, M. I.; Robertson, D. W. The body's potassium channels. *CHEMTECH* **1990**, 432–438.

(3) Edwards, G.; Weston, A. H. Structure–activity relationships of K^+ channel openers. *Trends Pharmacol. Sci.* **1990**, *11*, 417–422.

(4) Ashwood, V. A.; Cassidy, F.; Coldwell, M. C.; Evans, J. M.; Hamilton, T. C.; Howlett, D. R.; Smith, D. M.; Stemp, G. Synthesis and Antihypertensive Activity of 4-(Substituted-carbonylamino)-2*H*-1-benzopyrans. *J. Med. Chem.* **1990**, *33*, 2667–2672.

(5) Bergmann, R.; Gericke, R. Synthesis and Antihypertensive Activity of 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyrans and Related Compounds, New Potassium Channel Activators. *J. Med. Chem.* **1990**, *33*, 492–504.

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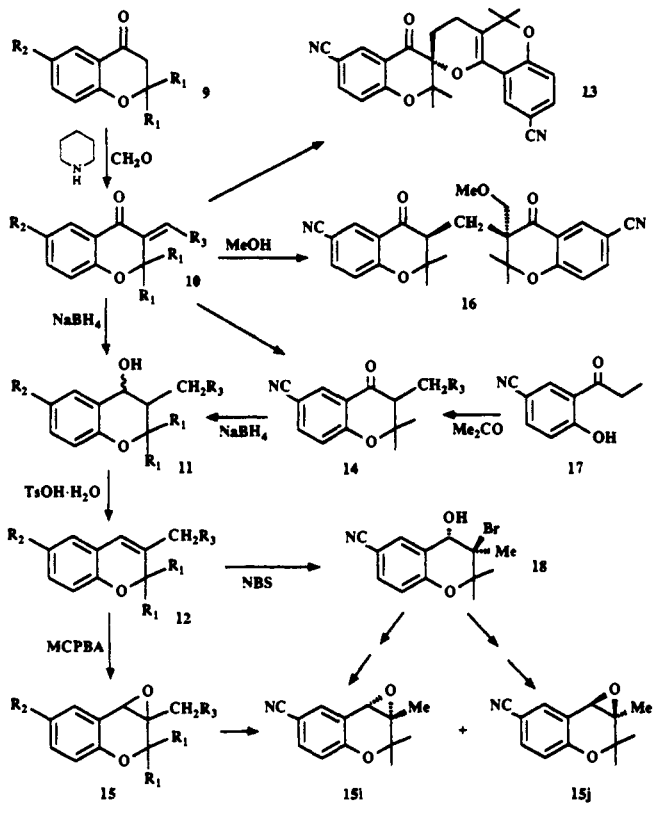
Scheme I



case of bimakalim (EMD 52 692; **3**) and Ro 31-6930 (**4**), the asymmetric centers are missing due to the unsaturation in the chromene ring. The chromanols SDZ PCO 400 (**5**) and EMD 57 283 (**6**)[6] both have an oxygen bridge at position 4 in common. Variations in the 6- and 7-positions of the chromanol are present in further substances under development: WAY-120,491 (**7**) and NIP-121 (**8**).[7] All substances developed subsequent to **1** exhibit higher potency in preclinical studies. We have been able to demonstrate that in some cases the potency of the potassium channel activators is increased further by an additional 3-methyl group in the 3-hydroxy-2*H*-1-benzopyran framework.

Chemistry

3,4-Epoxy intermediates **15** used in the preparation of the novel 4-substituted 3-methyl-2*H*-1-benzopyran compounds are new. The synthesis started from 4-chromanones **9**.[5] All attempts to introduce the 3-alkyl group directly were unsuccessful. However, the piperidine-catalyzed aldol condensation with paraformaldehyde[8] in alcohol led to the methylene compounds **10a**, **10e**, and **10f** (Scheme I; only the relative stereochemistry is shown, with the exception of **15i** and **15j**). This condensation was also possible with benzaldehyde (→**10g**), but not with acetaldehyde and higher homologues. Compounds **10** could be reduced easily with sodium borohydride in methanol to yield 3-methyl- and 3-benzyl-4-chromanols (R_3 = H, Ph). Chromanols **11** were formed as mixtures of poorly crystallizing diastereomers. It proved advantageous to convert the chromanol mixture directly to chromenes **12** (R_3 = H, Ph), especially since both asymmetric centers were lost during acid-catalyzed dehydration.

Methylene ketone **10a** was unstable in solution. If reduction was not carried out immediately, considerable quantities of Diels–Alder dimer **13**[9] were formed. **10** also was a good Michael-acceptor. For example, nitromethane was added easily to **10a** in a sodium methylate catalyzed reaction (→**14h**). Therefore it was no surprise that addition also took place with the base (piperidine → **14c**) used in the aldol condensation as well as with the solvent (ethanol → **14b**, benzyl alcohol → **14d**). The attempted addition of methanol to **10a** using sodium methylate as catalyst was unsuccessful, since the dimer form **16**[9] was produced preferentially. Some of the products shown in Scheme I were obtained in small quantities only and were difficult to isolate. However, as their consecutive products play a major part in the structure/activity relationships, they should not go unmentioned.

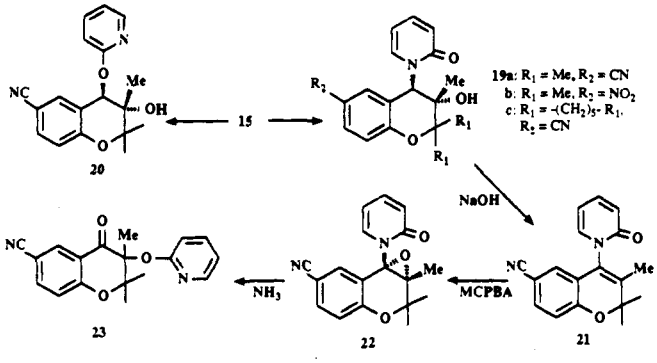
Principally the pyrrolidine-catalyzed synthesis of 3-methyl-4-chromanones starting with *o*-hydroxypropiophenones instead of *o*-hydroxyacetophenones was an attractive alternative to the described route via **9**, because the problematic methylation could be avoided. Kabbe et al.[10] however have already indicated that the yield in this reaction was low. Indeed, using, for example, acetone compound **17**[11] (readily prepared by Fries rearrangement of 4-cyanophenyl propionate) cyclized slowly and with poor yield (ca. 20%) to chromanone **14a**. Further conversion to chromene **12a** by sodium borohydride reduction and dehydration was successful.

With the exception of piperidinyl compound **12c**, all chromene compounds **12** underwent epoxidation with 3-chloroperbenzoic acid. Epoxides **15** were obtained as racemates. For the preparation of enantiomers of 3,4-dihydro-3,4-epoxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (**15i** and **15j**), the route via bromohydrin **18** was chosen.[12] The 4-camphanates of **18** were prepared from (+)-camphanic acid chloride. From this mixture it was possible to crystallize one diastereomer in pure form. This gave (−)-(3*S*,4*S*)-epoxide **15i** on alkaline hydrolysis. Correspondingly, (+)-(3*R*,4*R*)-epoxide **15j** was obtained with (−)-camphanic acid chloride. In analogy to the corresponding nonalkylated 3,4-dihydro-3,4-epoxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile enantiomers,[12] the assignment of the absolute configuration of **15i** and **15j** was possible (a) by their direction of rotation, (b) by comparison of their pharmacological activity, (c) by the elution sequence of the enantiomers on a chiral chromatographic phase,[13] and (d) by the elution sequence of the (1*S*)-camphanate precursors on silica gel.[12]

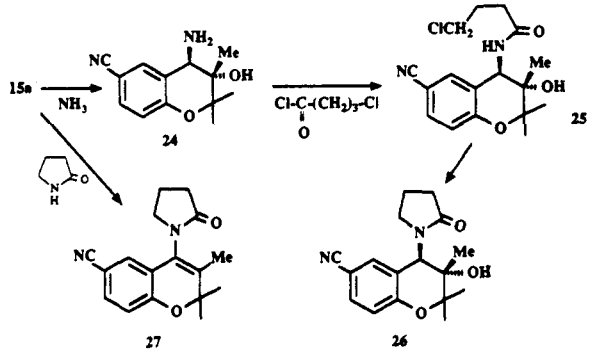
With the pure enantiomers **15i** and **15j** in hand it was

(6) Bergmann, R.; Eiermann, V.; Gericke, R. 4-Heterocyclyloxy-2*H*-1-benzopyran Potassium Channel Activators. *J. Med. Chem.* **1990**, *33*, 2759–2767.
(7) Masuda, Y.; Arakawa, C.; Miyajima, M.; Takeguchi, M.; Yamashita, T.; Tanaka, S. Effects of a novel potassium channel opener, NIP-121, on the rat aorta and portal vein. *Jpn. J. Pharmacol.* **1990**, *52*, Suppl 1, Abstr O-107.
(8) Anastasis, P.; Brown, P. E.; Islam, Q.; Marcus, W. Y. Studies of Chromenes. Part 7. Product Stabilization in Condensations with 7-Methoxy-2,2-dimethylchroman-4-one. *J. Chem. Res. (S)* **1989**, 36–37.
(9) Structure verified by X-ray diffraction.
(10) Kabbe, H.-J.; Widdig, A. Syntheses and reactions of 4-chromanones. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 247–255.
(11) Ramsden, C. A.; Knowles, P.; Lewis, E. J.; Lunt, E.; Wright, D. E. German Patent DE 2846931, 1977.
(12) Blarer, S.; UK Patent Appl. GB 2204868, 1988.
(13) Cabrera, K., unpublished results.

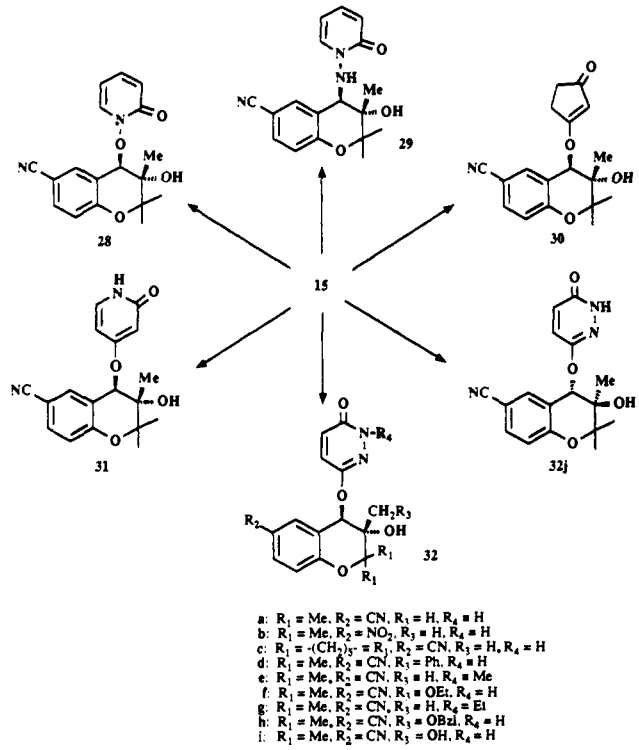
Scheme II



Scheme III



Scheme IV



possible to carry out the resolution by entrainment because **15a** is a conglomerate. To achieve this, a saturated THF solution of **15a** was seeded with **15i**, whereupon a small quantity of pure **15i** crystallized. Subsequently, **15j** was obtained from the solution by entrainment. Then the crystallization cycle started again with **15i**. In order to be able to work with constant quantities, the crystallized quantities of the respective enantiomer were replaced by the racemate **15a** each time. After several cycles, the yield of the desired enantiomer per crystallization step increased to 7%.

Epoxides **15a**, **15e**, and **15f** on treatment with 2-pyridinol and pyridine as base in refluxing ethanol led to (±)-*trans*-4-(1,2-dihydro-2-oxo-1-pyridyl)chromanols **19a–c** together with (±)-*trans*-4-(2-pyridyloxy)chromanols (e.g. **20**) (Scheme II; only relative stereochemistry is shown). Considerably more forcing reaction conditions were required to open epoxides **15** (e.g. several days reflux) in contrast to the corresponding demethyl compounds.[5] Also in contrast to the demethyl series, where O-substitution is of minor importance, here both products **19** and **20** were formed in almost equal proportions. On silica gel chromatography, N-substituted products **19** always eluted after the oxygen bridge containing isomers. Compound **19a** was dehydrated with sodium hydroxide in dioxane, chromene **21** epoxidized with 3-chloroperbenzoic acid, and epoxide **22** rearranged with ammonia in good yield to (pyridyloxy)chromanone **23**. An analogous reaction sequence was described recently for the corresponding demethyl compounds.[5]

Reaction of epoxide **15a** with 2-pyrrolidinone using the conditions described by Evans et al.[14] (NaH, DMSO) resulted in the exclusive formation of chromene **27** (Scheme III). The tendency toward dehydration, usually present under basic reaction conditions, was considerably more pronounced within the 3-methyl series. In the preparation of 3-methylcromakalim **26** the following alternative route, also described in the above-mentioned publication, was chosen: 4-Aminochromanol **24** was formed from epoxide **15a** by treatment with NH_3; this was then acylated with 4-chlorobutyryl chloride to intermediate **25** which subsequently cyclized intramolecularly with K_2CO_3/KI to the desired product **26**.

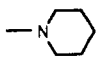
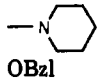
The active compounds **5** and **6** show that the ring on position 4 can also be connected by an oxygen bridge. Structures **28** and **29** (Scheme IV; only one tautomeric form is shown) represent a new variation with the oxygen and nitrogen bridges respectively attached directly to the N atom of α-pyridone. 1,2-Dihydro-1-hydroxypyridin-2-one[15] and 1-amino-1,2-dihydropyridin-2-one[16] served as building blocks for the synthesis. Compound **29** was prepared, in contrast to the standard procedure, by melting together the aminopyridone and epoxide **15a**. In analogy to compound **5**, **30** was prepared with 1,3-cyclopentanedione/NaH/BF_3·Et_2O in THF according to the synthesis described by Blarer.[12] It was recently reported that 2,4-dihydroxypyridine and 3,6-pyridazinediol did not give the expected N-substituted products, rather the isomeric 4-(heterocyclyloxy)chromanols were formed.[6] Thus, the 4-[(1,2-dihydro-2-oxo-4-pyridyl)oxy] compound **31** was obtained from 2,4-dihydroxypyridine and epoxide **15a** in ethanol and pyridine. The enantiomeric 4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy] compounds **32a** and **32j** were prepared from epoxides **15i** and **15j** and 3,6-pyridazinediol. Synthesis of compounds **32b–d,f,h** was carried out with the epoxides shown in Scheme I. Derivatives **32e** and **32g** were prepared by N-alkylation of the racemic compound **32a**, and the debenzylation of **32h** to

(14) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. Synthesis and Antihypertensive Activity of 4-(Cyclic amido)-2*H*-1-benzopyrans. *J. Med. Chem.* **1986**, *29*, 2194–2201.

(15) Newbold, G. T.; Spring, F. S. Hydroxamic Acids. Part I. Cyclic Hydroxamic Acids Derived from Pyridine and Quinoline. *J. Chem. Soc.* **1948**, 1864–1866.

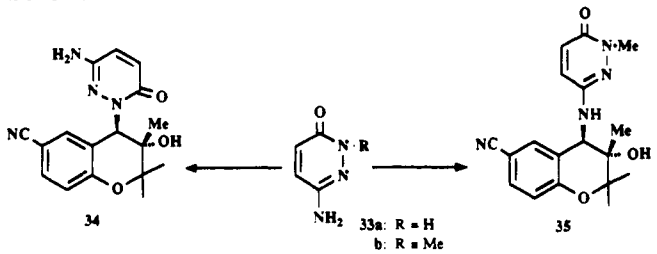
(16) Hoegerle, K.; Erlenmeyer, H. Reaction of α-pyridone with chloramine. *Helv. Chim. Acta* **1956**, *39*, 1203–1207.

Table I. 3-Substituted Chromanones 10 and 14, Chromenes 12, and 3,4-Epoxychromans 15

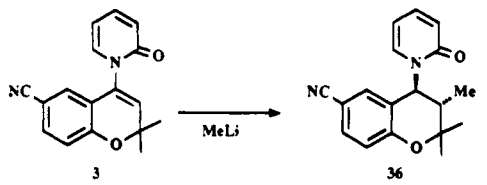
no.	R_1	R_2	R_3	% yield	mp, °C	recryst solvent	formula[a]
10a	Me	CN	H	20	105–107	$(Me_2CH)_2O$	$C_{13}H_{11}NO_2$
10e	Me	NO_2	H	38	105–107	$(Me_2CH)_2O$	$C_{12}H_{11}NO_4$
10f	$-(CH_2)_5-$	CN	H	32	240–241	petroleum ether	$C_{18}H_{15}NO_2 \cdot 0.25H_2O$
10g	Me	CN	Ph	33	95–97	$(Me_2CH)_2O$	$C_{19}H_{15}NO_2 \cdot 0.25H_2O$
12a	Me	CN	H	33[b]	60–61.5	petroleum ether	$C_{13}H_{13}NO$
12b	Me	CN	OEt	46[c]	37–39	petroleum ether	$C_{15}H_{17}NO_2 \cdot 0.75H_2O$
12c	Me	CN		2[b]	116–119	Me_2CHOH	$C_{18}H_{22}N_2O$
12d	Me	CN	OBzl	3[b]	67–69	petroleum ether	$C_{20}H_{19}NO_2 \cdot 0.25H_2O$
12e	Me	NO_2	H	8[b]	49–50	petroleum ether	$C_{12}H_{13}NO_3 \cdot 0.25H_2O$
12f	$-(CH_2)_5-$	CN	H	33[b]	99–100.5	petroleum ether	$C_{16}H_{17}NO \cdot 0.25H_2O$
12g	Me	CN	Ph	9[b]	166–167	$(Me_2CH)_2O$	$C_{19}H_{17}NO \cdot 0.25H_2O$
12h	Me	CN	CH_2NO_2	33[c]	80–82	$(Me_2CH)_2O$	$C_{14}H_{14}N_2O_3$
14a			H	17	128–130	$(Me_2CH)_2O$	$C_{13}H_{13}NO_2$
14b			OEt	8[b]	89–90	$(Me_2CH)_2O$	$C_{15}H_{17}NO_3$
14c[d]				9[b]	234	H_2O	$C_{18}H_{22}N_2O_2 \cdot HCl \cdot 0.5H_2O$
14d			OBzl	3[b]	67–68	Me_2CHOH	$C_{20}H_{19}NO_3$
14h			CH_2NO_2	56	185–187	Me_2CHOH	$C_{14}H_{14}N_2O_4$
15a	Me	CN	H	96	121–123	$(Me_2CH)_2O$	$C_{13}H_{13}NO_2$
15b	Me	CN	OEt	60	oil	-	$C_{15}H_{17}NO_3 \cdot 0.25H_2O$
15d	Me	CN	OBzl	97	63–65	$(Me_2CH)_2O$	$C_{20}H_{19}NO_3 \cdot 0.5H_2O$
15e	Me	NO_2	H	66	80–82	$(Me_2CH)_2O$	$C_{12}H_{13}NO_4$
15f	$-(CH_2)_5-$	CN	H	68	121–122	$(Me_2CH)_2O$	$C_{16}H_{17}NO_2$
15g	Me	CN	Ph	44	108–110	$(Me_2CH)_2O$	$C_{19}H_{17}NO_2 \cdot 0.25H_2O$
15h	Me	CN	CH_2NO_2	67	100–102	EtOAc	$C_{14}H_{14}N_2O_4$
15i				20	153–155	$(Me_2CH)_2O$	$C_{13}H_{13}NO_2$
15j				24	154–156	$(Me_2CH)_2O$	$C_{13}H_{13}NO_2$

[a] All C, H, N analyses were within ±0.4% of the theoretical values. [b] Overall yield from 9. [c] Overall yield from 14. [d] Because of instability, characterized as hydrochloride.

Scheme V



Scheme VI



32i was achieved by catalytic transfer hydrogenation with ammonium formate.[17]

It was reported recently[6] that epoxide ring opening with heterocycle 33a[18] gave a 4-(3-amino-1,6-dihydro-6-oxo-1-pyridazinyl) derivative lacking the NH bridge. Compound 34 was prepared accordingly with epoxide 15a (Scheme V). The methyl derivative 33b was readily prepared from 33a with methyl iodide. It only could react through its nucleophilic NH_2 group. Accordingly, the 4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)amino] compound 35 was formed with 15a. In contrast to 6 (besides the additional 3-methyl group), the oxygen bridge was replaced by a NH bridge.

The addition of organometallic compounds as lithium dialkyl copper reagents to Michael systems is well-documented.[19] In our hands methyl lithium in THF added to chromene 3 to form the trans-configurated compound 36[9] in moderate yield (Scheme VI). We assume that the double bond in 3 was sufficiently activated by the cyano-substituted benzene ring and that the pyridone carbonyl group assisted the insertion of the methyl group by coordination.

Results and Discussion

The hyperpolarizing (ΔmV) and antispasmodic or relaxing (IC_{50}) effects of the compounds were determined in organ-bath studies using pig coronary arteries precontracted with acetylcholine, or rabbit main pulmonary arteries precontracted with noradrenaline. Membrane potential was recorded by using a conventional microelectrode technique. The 3-methyl-2*H*-1-benzopyrans listed in Table II represent a new group of potassium channel activators. They could be prepared by using methods similar to those for the demethyl analogues. The comparison of potencies of both groups leads to surprising results.

Compounds 19–22 in Scheme II are only weakly active. In the case of 4-(2-pyridyloxy) compound 20 this is not surprising: The corresponding demethyl compound[5] has been described as an inactive antihypertensive compound. Demethyl analogues of 19a and 21, however, are compounds EMD 56 431 (2) and bimakalim (3) under development. As the corresponding demethyl compounds of 19b and 22 also have been described to possess a high antihypertensive activity, it is clear that in the 3-methyl-4-(1,2-dihydro-2-oxy-1-pyridyl) series the drop in activity is due to the introduction of the 3-methyl group. Substances 26 and 27 shown in Scheme III are the 3-

(17) Ram, S.; Spicer, L. D. Debenzylation of *N*-benzylamino derivatives by catalytic transfer hydrogenation with ammonium formate. *Synth. Commun.* **1987**, *17*, 415–418.
(18) Horie, T.; Kinjo, K.; Ueda, T. Pyridazine derivatives. I. Synthesis and antimicrobial activity of 6-substituted 3-aminopyridazine and its sulfonamido derivatives. *Chem. Pharm. Bull.* **1962**, *10*, 580–591.
(19) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons; New York, 1985; pp 713–717.

Table II. Compounds of Schemes II–VI

no.	% yield	mp, °C	recryst solvent	formula	anal.[a]	hyperpolarization Δ, mV	hyperpolarization conc,[c] μM	relaxation IC_{50},[d] μM
1						28	3	0.7
2						34	1	0.3
3						23	0.1	0.05
6						29	0.1	0.05
19a	30	185–186	EtOAc	$C_{18}H_{19}N_2O_3$	C, H, N	19	100	NE[e]
19b	18	220–222	MeCN	$C_{17}H_{18}N_2O_5$	C, H, N	22	10	20
19c	5	204–206	Et_2O	$C_{21}H_{22}N_2O_3$	C, H, N	3	100	20
20	34	105–107	$(Me_2CH)_2O$	$C_{18}H_{18}N_2O_3$	C, H, N	25	100	6
21	64	210–212	Me_2CHOH	$C_{18}H_{16}N_2O_2$	C, H, N	29	100	5
22	47	176–178	Et_2O	$C_{18}H_{16}N_2O_3 \cdot 0.25H_2O$	C, H, N	10	100	NE
26	71	195–197	Me_2CHOH	$C_{17}H_{20}N_2O_3 \cdot 0.5H_2O$	C, H, N	23	10	4
27	50	184–186	EtOAc	$C_{17}H_{18}N_2O_2$	C, H, N	29	100	NE
28	43	175–177	EtOAc	$C_{18}H_{18}N_2O_4 \cdot 0.25H_2O$	C, H, N	21	100	NE
29	15	184–187	Me_2CHOH	$C_{18}H_{19}N_3O_3$	C, H, N	12	100	NE
30	24	204–206	Me_2CHOH	$C_{18}H_{19}NO_4$	C, H, N	25	1	0.02
31	50	214	EtOAc	$C_{18}H_{18}N_2O_4 \cdot 0.75H_2O$	C, H, N	35	0.1	0.004
32a	86	135	EtOAc	$C_{17}H_{17}N_3O_4 \cdot 0.25H_2O$	C, H, N	29	0.1	0.006
32b	37	223–225	EtOH	$C_{16}H_{17}N_3O_6 \cdot 0.25H_2O$	C, H, N	24	0.1	0.02
32c	7	>275	MeOH	$C_{20}H_{21}N_3O_4 \cdot 0.5H_2O$	C, H, N	26	100	80
32d	2	242–243	Et_2O	$C_{23}H_{21}N_3O_4$	C, H, N	6	100	NE
32e	86	197–199	Me_2CHOH	$C_{18}H_{19}N_3O_4$	C, H, N	24	0.1	0.03
32f	55	217–219	Me_2CHOH	$C_{19}H_{21}N_3O_5$	C, H, N	12	100	50
32g	73	166–168	Me_2CHOH	$C_{19}H_{21}N_3O_4$	C, H, N	22	0.1	0.007
32h	56	194–196	Me_2CO	$C_{24}H_{23}N_3O_5 \cdot 0.25H_2O$	C, H, N	16	100	NE
32i	20	212–215	Me_2CHOH	$C_{17}H_{17}N_3O_5$	C, H; N[f]	32	3	0.7
32j	63	135	EtOAc	$C_{17}H_{17}N_3O_4 \cdot 0.25H_2O$	C, H, N	20	100	100
34	12	244	Me_2CHOH	$C_{17}H_{18}N_4O_3$	C, H, N	13	100	40
35	20	258–260	EtOAc	$C_{18}H_{20}N_4O_3$	C, H, N	34	0.1	0.02
36	32	182–185	Et_2O	$C_{18}H_{18}N_2O_2$	C, H, N	10	1	NE

[a] Analyses for the elements indicated were within ±0.4% of the theoretical values. [b] Magnitude of hyperpolarization of smooth muscle cells of the rabbit main pulmonary artery. Each value is the average of two preparations. [c] Drug concentration examined. [d] Drug concentrations required to inhibit acetylcholine-induced concentrations in pig coronary arteries by 50%. Each value is the average of two preparations. [e] Compounds with IC_{50} values > 100 μM. [f] N: calcd, 12.24; found, 11.49.

methyl analogues of cromakalim (1) and its corresponding dehydration product. As in the case of the pyridone compounds, the additional methyl group is responsible for the drastic reduction in potency. This applies to the chromanol as well as to the chromene residue.[14]

An additional 3-methyl group does not always lead to a reduction in potency. This is shown by the series of products in Scheme IV. In contrast to the compounds discussed so far, the (heterocyclic) ring at position 4 is not attached directly but via an oxygen or NH bridge. Compounds **28** and **29** differ from **19a** only by this additional oxygen or NH bridge; they are both either weakly potent or inactive. However compound **30**, the 3-methyl analogue of compound **5**, is very potent. In contrast to the substances discussed so far; its antispasmodic potency is greater by at least a factor of 100.

Compound **31** is even more potent; it has a maximum hyperpolarizing effect of 35 mV at a concentration of 0.1 μM, and the IC_{50} value for its relaxing effect is 0.004 μM. To our knowledge, (±)-3,4-dihydro-4-[(1,2-dihydro-2-oxo-4-pyridyl)oxy]-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (**31**) is the most potent potassium channel activator known to date. Comparing the effect on blood vessels, it is 100 times more potent than cromakalim and 10 times more potent than bimakalim and EMD 57 283 (**6**). The demethyl analogue of compound **31** was recently established as the most powerful antihypertensive derivative of the 4-(heterocyclyloxy)-2*H*-1-benzopyran series.[6] It is shown here that the introduction of the methyl group increased considerably further its hyperpolarizing, antispasmodic, and antihypertensive potencies.[20] Of similar high potency as **31** is 3-methyl-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy] compound **32a**. The corresponding demethyl analogue of **32a** also was described as a potent hypotensive agent.[6] The levorotatory enantiomer **32a** is more than 1000 times more potent than the corresponding dextrorotatory enantiomer **32j** regarding hyperpolarization and relaxation.

The high efficacy of **32a** is largely retained after alkylation of the pyridazinone nitrogen atom (→**32e** and **32g**) or substitution of the electron-withdrawing 6-cyano group by a nitro group (→**32b**). These results are very similar to those observed in the demethyl series.[6] Other variations lead to a strong reduction in potency as exemplified by compound **32c**, where the geminal 2-methyl groups of **32a** are replaced by a spiro ring. Substitution of the 3-methyl group by benzyl (→**32d**), ethoxymethyl (→**32f**), and (benzyloxy)methyl groups (→**32h**) leads to an almost complete loss of potency. Only in the case of the 3-hydroxymethyl group, medium potency was retained (**32i**). These findings support the view that groups larger than methyl are disadvantageous.

In analogy to the 3-demethyl series,[6] epoxide ring opening with heterocycle **33a** resulted in the poorly active 4-(3-amino-1,6-dihydro-6-oxo-1-pyridazinyl) compound **34**. On the contrary, similar treatment of methyl derivative **33b** provided the very interesting new 4-(heterocyclylamino)-2*H*-1-benzopyran structure **35**. In contrast to compound **32a**, the oxygen bridge has been substituted by a nitrogen bridge. Bearing in mind that **32a** is an enantiomer and **35** a racemate, it can be stated that both compounds possess approximately the same high potency. The new structure of compound **36** shown in Scheme VI can be compared best with that of compound **2**, where the hydroxyl group has been replaced by a methyl group. Any analogy to compound **19a** is only partly valid, as the pyridone and methyl groups are cis-configurated in **19a** whereas they are in a trans arrangement in **36**. Compound

(20) Bergmann, R.; Harting, J.; Lues, I., unpublished results.

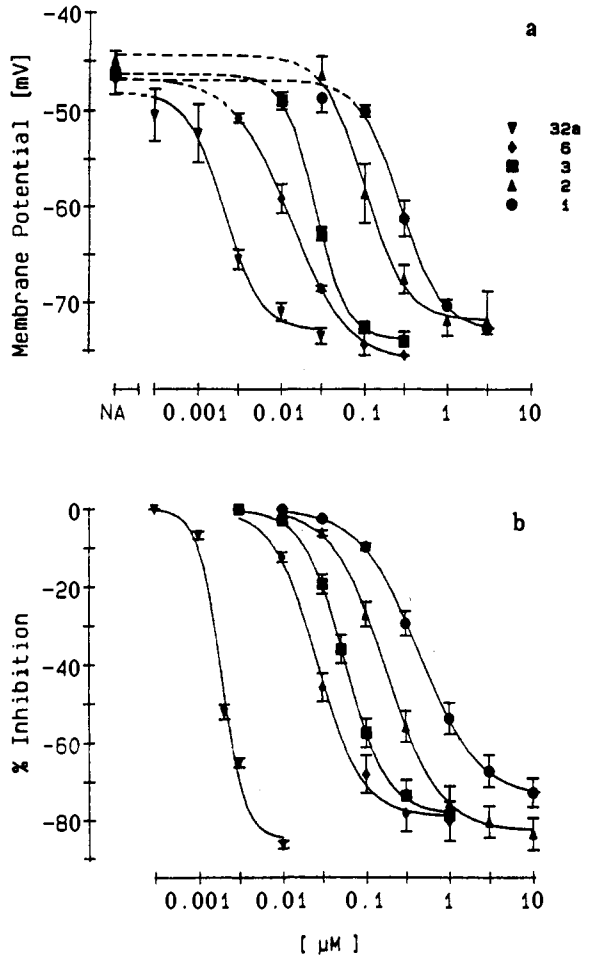


Figure 1. Hyperpolarizing (a) and relaxing (b) effects of various compounds as indicated in the figure determined in different experiments using rabbit main pulmonary arteries precontracted with 0.7–1 μM noradrenaline (NA). Given are mean values ± SEM from four to six preparations for each compound.

Table III. EC_{50} and IC_{50} Values of Selected Compounds

no.	hyperpolarization EC_{50}[a] (CL_{95}[b]), nM	relaxation IC_{50}[c] (CL_{95}[b]), nM
1	263 (154–451)	420 (330–550)
2	105 (48–230)	174 (120–250)
3	27 (20–37)	57 (46–71)
6	11 (6–21)	26 (21–32)
32a	3 (1–5)	2 (1.7–2.0)

[a] Drug concentration required to induce half maximal hyperpolarization in rabbit main pulmonary arteries. [b] 95% confidence limits. [c] Drug concentrations required to inhibit noradrenaline-induced contractions in rabbit main pulmonary arteries by 50%.

36 exhibits a modest potency only.

For the selected compound **32a**, as well as for the reference substances **1**, **2**, **3**, and **6**, the potency (EC_{50} values) of the hyperpolarizing and relaxation effects were additionally measured in the rabbit main pulmonary artery (RMPA). The concentration/response curves for hyperpolarization and relaxation are shown in Figure 1; the corresponding EC_{50} and IC_{50} values are summarized in Table III.

Pretreatment of the arterial strip with noradrenaline depolarizes the membrane potential of the pulmonary artery smooth muscle cells from about −55 to about −45 mV (Figure 1a). The test substances induced a concentration-dependent re- or hyperpolarization of the membrane potential to values of between −70 and −75 mV. For bimakalim (**3**), it has been shown that the hyperpolarization was caused by activation of glibenclamide-sensitive potassium channels.[21] Within the same concentration range, the substances induced a relaxation of the precontracted arterial strips (Figure 1b). The concentrations for the half-maximal hyperpolarizing (EC_{50}) and relaxing (IC_{50}) effects, which are determined in different experiments, are closely correlated (Table III). The high degree of parallelism between hyperpolarization and relaxation suggested that there is a causal relationship between both effects. The order of potency is **32a** > **6** > **3** > **2** > **1**. Compound **32a** is about 100 times more potent than cromakalim. The concentration/response curves for all substances are very steep. The maximum effective concentration is only about one power of 10 above the threshold value.

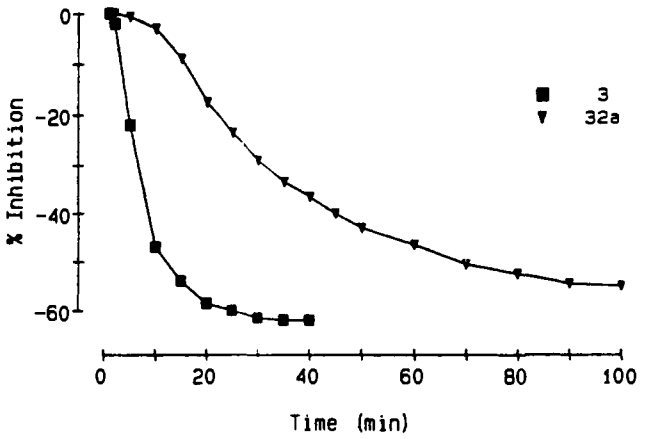


Figure 2. Time course of the relaxing effects of compounds **3** (0.06 μM) and **32a** (0.005 μM) in the rabbit main pulmonary artery precontracted with noradrenaline.

Compound **32a** (and also the other 3-methyl compounds) differed markedly from the reference compound **3** with respect to the time course of action in vitro. At equieffective concentrations **32a** displayed a much slower onset and development of action than did compound **3**. The half-life times of the relaxing effects shown in Figure 2 for compounds **32a** and **3** differ by a factor of about 5 (**3**, 7 min vs **32a**, 30 min). The same differences in the kinetics were obtained with respect to the hyperpolarizing effects of these compounds (data not shown). In addition, the reversibility of the effect (washout) was substantially different for both substances; for **3** washout was complete within a few minutes while for **32a** it took 2–3 h. The reason for these differences in kinetic behavior are virtually unknown. They might be due to differences in the physicochemical properties of the compounds which influence their interaction with the target structure.

The differences described here in the kinetics of compound **32a** compared to other classical chroman derivatives are also reflected in in vivo experiments: The hemodynamic effects of compound **32a** after iv administration developed much more slowly than, for example, with substance **3**, and the effect lasts much longer. This moderate development of action in vivo is a beneficial property of the compound as it thus avoids pronounced undesired counterregulation. Further work is going on to evaluate the pharmacodynamic and pharmacokinetic profile of this compound in more detail.

Conformation/Activity Relationships

The results of the structure/activity relationships are puzzling to some extent. While, for the 4-(heterocyclyloxy)

(21) Gericke, R.; Lues, I.; de Peyer, J.-E.; Häusler, G. Electrophysiological and pharmacological characterization of EMD 52 692, a new potassium channel activator. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, Suppl 339, Abstract 247.

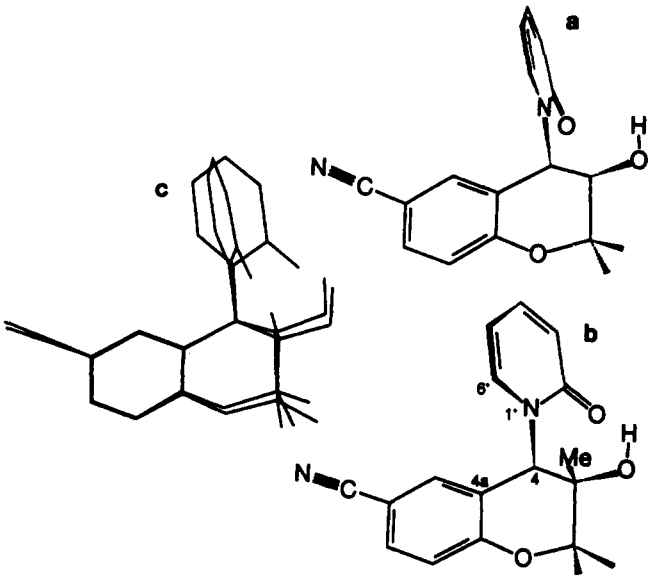


Figure 3. X-ray crystal structures of compounds 2 (a) and 19a (b) and the superimposition of both structures (c).

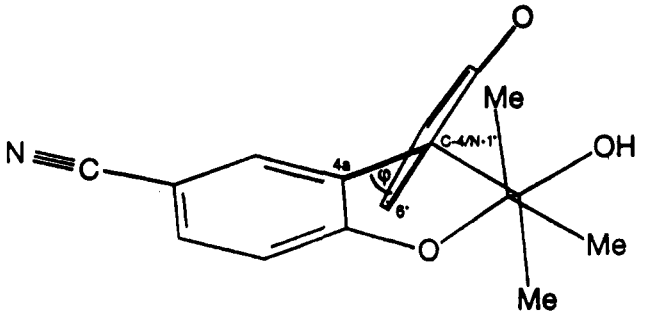


Figure 4. X-ray crystal structure of compound 19a. This is represented in such a way that C-4 and N-1′ meet at one point and form the vertex of the torsion angle φ between the centers C-4a/C-4/N-1′/C-6′. The pyridone ring lies above the benzopyran system.

compounds, the activity increases strongly on incorporation of the 3-methyl group (e.g. **6** → **32a**), the same variation in the classical series leads to a considerable loss of potency (e.g. **1** → **26**, **2** → **19a**, **3** → **21**). These fundamental differences between the two series are difficult to understand, especially as no functionality is provided by a methyl group. Therefore we have investigated the effects of the methyl group on the conformation of the molecules. A conformational change most probably would supply the key to understanding this phenomenon.

In order to determine the conformation in the crystal, X-ray structural analyses of several selected substances were carried out (Table V). The orientation of the C-4 substituent seems to be of prime importance. Evans et al. found for cromakalim (1) an orthogonal arrangement of the pyrrolidinone with respect to the benzopyran ring system.[22] The representation chosen for 1 shows the carbonyl group pointing backwards. Very similar observations were made with 2 (Figure 3a). In contrast, methyl compound **19a** (Figure 3b) shows a conformation with the pyridone ring more in the plane of the benzopyran skeleton, although the carbonyl group is still pointing backwards. The differences between the two structures become particularly apparent on superimposition (Figure 3c). In

(22) Cassidy, F.; Evans, J. M.; Smith, D. M.; Stemp, G.; Edge, C.; Williams, D. J. Conformational Analysis of the Novel Antihypertensive Agent Cromakalim (BRL34915). *J. Chem. Soc., Chem. Commun.* **1989**, 377–378.

Table IV. Torsion Angles and Interplanar Angles of Selected Compounds

no.	torsion angle φ,[a] deg	interplanar angle ξ,[b] deg	no.	torsion angle φ,[a] deg	interplanar angle ξ,[b] deg
1	63.3[c]	102.3[d]	**19a**	34.7	121.3
2	70.3	93.6	**32a**		101.4
3	79.9	97.0	**36**	52.5	101.3
6		83.7			

[a] Torsion angle between centers C-4a/C-4/N-1′/C-6′. [b] Angle between planes of the phenyl ring and heterocyclic ring in position 4. [c] Torsion angle between centers C-4a/C-4/N-1′/C-5′. [d] The plane of the pyrrolidinone ring is defined by centers N-1′, C-2′, and C-3′.

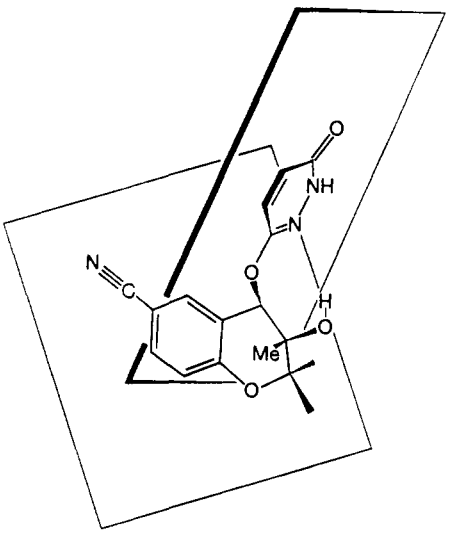


Figure 5. X-ray crystal structure of compound **32a**. The emphasized planes as well as all other three-dimensional representations were obtained with the program SYBYL (Tripos) and subsequently graphically refined. The planes of the phenyl and pyridazinone rings intersect at angle ξ.

order to study the different positions of the pyridone rings more exactly, the angles φ of the C-4/N-1′ torsion were investigated. In Figure 4, **19a** is represented in such a way that atoms C-4 and N-1′ meet in one point; the pyridone ring is located above the benzopyran. The torsion angle φ formed from the four centers C-4a/C-4/N-1′/C-6′ amounts to 34.7°. Table IV summarizes the torsion angles of additional selected compounds taken from the set of X-ray data. For the series **19a** → **36** → **1** → **2** → **3**, φ increases from 34.7° to 79.9°. Interestingly the pharmacological activity also increases in the same sequence. Due to freedom of rotation around two bonds, torsion angles cannot be used to define the relative orientation of the ring systems for heterocyclyloxy compounds **6** and **32a**. It seems desirable however to include these compounds in the conformation/response considerations, because in the crystal structure they also have the ring systems arranged virtually orthogonally with respect to each other. This is illustrated for compound **32a** in Figure 5, where the planes of the phenyl ring on the one hand and of the pyridazinone ring on the other hand are emphasized. The nitrogen atoms of the pyridazinone are pointing backwards in this illustration. With a vector calculation, an intersecting angle ξ of 101.4° between the two planes was determined (Table IV).

The interplanar angles ξ for the other compounds investigated are within the range of 83.7° to 121.3°. In this series **19a** shows the weakest pharmacological activity and possesses the largest angle ξ. In fact, for **19a**, ξ is almost 28° larger than for the corresponding highly active de-

Table V. Crystal Data for Compounds 2, 3, 6, 19a, 32a, and 36

	2	3	6	19a	32a	36
formula	$C_{17}H_{16}N_2O_3$	$C_{17}H_{14}N_2O_2$	$C_{17}H_{17}N_3O_4$	$C_{18}H_{18}N_2O_3$	$C_{17}H_{17}N_3O_4 \cdot 0.5EtOAc$	$C_{18}H_{18}N_2O_2$
mol wt	296.33	278.31	327.34	310.36	371.43	294.38
system	monoclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic
space group	$P2_1/n$	$C2/c$, no. 15	$P2_1/c$	$P\bar{1}$	$P2_1/n$	$P2_1/n$
a, pm	887.9 (2)	1429.6 (3)	1168.9 (3)	944.1 (2)	1675.2 (2)	958.0 (1)
b, pm	1805.3 (3)	971.1 (4)	1099.8 (4)	1200.2 (2)	1415.8 (2)	1591.4 (1)
c, pm	923.7 (2)	2083.4 (4)	1246.2 (4)	712.6 (2)	1712.1 (3)	1071.1 (1)
α, deg	90	90	90	94.47 (2)	90	90
β, deg	101.43 (3)	95.935 (7)	91.51 (4)	99.75 (2)	106.89 (3)	107.58 (1)
γ, deg	90	90	90	82.93	90	90
V, pm^3	1451.3×10^6	2877.0×10^6	1601.6×10^6	788.3×10^6	3885.5×10^6	$1556.7\ (1) \times 10^6$
Z	4	8	4	2	8	4
ρ_x, g cm^{-3}	1.356	1.285	1.357	1.307	1.270	1.256
$F(000)$	624	1186	688	328	1568	624
μ(Cu Kα), cm^{-1}	7.310	0.800	0.922	6.946	0.872	6.281
reflections $I \geq 3\sigma(I)$	1681	1086	1977	2073	2641	2401
no. of refinement parameters	200	191	269	209	500	200
R	0.056	0.042	0.040	0.056	0.052	0.043
R_w	0.061	0.040	0.036	0.062	0.050	0.041

methyl compound 2. The methyl group also causes a distinct increase of the angle in the heterocyclyloxy series (6 vs 32a), but ξ remains within the normal range. It is also remarkable that chromanol 2 and chromene 3 show very few differences in either their torsion or their interplanar angles. The pyrrolidinone ring in compound 1 is not completely flat. The best fit between the planes of the pyrrolidinone and pyridone rings is reached by the centers N-1′, C-2′, and C-3′. With this definition, indeed an angle $\xi = 102.3°$ can be calculated for 1. This value is in the normal range.

All potassium channel activators investigated by us showed a similar conformation in the solid state. The heterocyclic rings are by and large in an orthogonal arrangement to the benzopyran system. The carbonyl groups and nitrogen atoms of the 4-heterocycle point backwards (when represented as in this paper). In addition, our investigations indicate that the pharmacological activity may depend upon the exact relative orientation of both ring systems. The incorporation of a methyl group consequently has a greater effect on the N-bound compounds than on those substances containing an oxygen bridge. While in the latter case the methyl group is not a disturbing factor and indeed may promote a favorable conformation on the receptor site, this conformation cannot be achieved in the former case. Further studies are necessary to ensure the general validity of these findings, and the number of substances examined should be increased to allow a more solid conclusion.

Whether the conformation in the crystalline state is relevant for the biological activity is an open question. Dissolved in a body fluid, drugs are transported to the receptor site where flexible molecules are able to adopt the biologically active conformation. According to ^{1}H NMR studies in various solvents performed by Thomas and Whitcombe,[23] potassium channel activators of the benzopyran type adopt a preferred conformation in solution. Nevertheless, due to low barriers of rotation around the bond connecting the heterocycle in position 4, a rapid rotation can be observed. Therefore it must be assumed that rapid rotation at room temperature for all chromenes, (heterocyclyloxy)chromanols, 1, and analogous compounds is possible. This contrasts to studies in DMSO where 4-pyridone chromanols of type 2 exhibited higher rotation barriers with coalescence points at about 80 °C.[6] This also applies to compound 36 as well as to 19a, surprisingly. While compound 2 in DMSO at room temperature produces a double set of almost equally strong but clearly separated signals, compound 19a shows an isomeric ratio of 92:8 with very similar chemical shifts. Possibly the pyridone ring of compound 19a possesses only a minor degree of rotational freedom. These results suggest a restricted rotation of this compound as explanation for the weak activity. The conformation required at the receptor site cannot be adopted. It can be speculated that there is a relation between conformations in the crystal, in solution, and at the receptor. Further investigation of these problems is necessary, as more findings about the receptor site of potassium channels will undoubtedly give new chemical and pharmacological insights.

(23) Thomas, W. A.; Whitcombe, W. A. Conformational Behaviour of Cromakalim and Related Potassium Channel Activators. *J. Chem. Soc., Chem. Commun.* **1990**, 528–529.

Experimental Section

Melting points were determined with a Büchi 535 melting point apparatus and are uncorrected. IR, NMR, and mass spectra are in agreement with the structures cited and were recorded on a Bruker IFS 48 IR spectrophotometer, a Bruker AC 200, WM 250, or AM 500 (TMS as internal standard), and a Vacuum Generators VG 70-70 or 70-250 at 70 eV, respectively. Crystal data were collected on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Cu Kα radiation. Microanalyses were obtained with a Perkin-Elmer 240B C, H, N analyzer. Precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from E. Merck, Darmstadt, Germany, were used for thin-layer chromatography.

3,4-Dihydro-2,2-dimethyl-3-methylene-4-oxo-2*H*-1-benzopyran-6-carbonitrile (10a). 3,4-Dihydro-2,2-dimethyl-4-oxo-2*H*-1-benzopyran-6-carbonitrile (9a; 12 g, 60 mmol), paraformaldehyde (6 g), and piperidine (12 mL, 121 mmol) were refluxed in EtOH (200 mL) for 6 h. The solution was evaporated and the resultant dark oil was chromatographed on silica gel. Elution with CH_2Cl_2 and evaporation of the combined nonpolar fractions gave a partially crystalline residue (14.5 g) that was treated with boiling $(Me_2CH)_2O$ (200 mL). The precipitate that formed (3.5 g, 28%) was separated from the solution, and a portion was recrystallized from Me_2CHOH to give 3′,4′-dihydro-2,2,5′,5′-tetramethyl-4-oxospiro[2*H*-1-benzopyran-3(4*H*),2′-[2*H*,5*H*]pyrano[3,2-*c*][1]-benzopyran]-6,9′-dicarbonitrile (13): mp 213–215 °C; NMR ($CDCl_3$) δ 1.45 (s, 6 H), 1.56 (s, 3 H), 1.59 (s, 3 H), 2.10 (m, 4 H), 6.81 (d, 7.4, 1 H), 7.09 (d, 8.5, 1 H), 7.40 (dd, 7.4, 1.4, 1 H), 7.44 (d, 1.4, 1 H), 7.75 (dd, 8.5, 2.1, 1 H), 8.10 (d, 2.1, 1 H). Anal. ($C_{26}H_{22}N_2O_4$) C, H, N. The $(Me_2CH)_2O$ mother liquor was evaporated, and the residue (11 g) was chromatographed on silica gel with CH_2Cl_2/petroleum ether mixtures using a gradient elution technique. The combined nonpolar fractions were evaporated and the gum was triturated with petroleum ether to give crude

methylene ketone **10a**: 2.5 g (20%). Recrystallization of a sample from $(Me_2CH)_2O$ gave **10a** as stable crystals: mp 105–107 °C; NMR ($CDCl_3$) δ 1.64 (s, 6 H), 5.69 (d, 0.5, 1 H), 6.39 (d, 0.5, 1 H), 7.05 (d, 10.0, 1 H), 7.73 (dd, 10.0, 2.0, 1 H), 8.30 (d, 2.0, 1 H). Anal. ($C_{13}H_{11}NO_2$) C, H, N. In certain instances, investigation of other chromatographic fractions or mother liquors from recrystallization revealed the presence of further byproducts; for example, **14c** and 3-ethoxymethyl-3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-1-benzopyran-6-carbonitrile (**14b**) were obtained in this manner. **14b**: mp 89–90 °C; NMR ($CDCl_3$) δ 1.15 (t, 7.1, 3 H), 1.45 (s, 3 H), 1.57 (s, 3 H), 2.91 (t, 6.3, 1 H), 3.49 (q, 7.1, 2 H), 3.71 (dd, 10.2, 6.3, 1 H), 3.89 (dd, 10.2, 4.2, 1 H), 7.02 (d, 8.5, 1 H), 7.70 (dd, 8.5, 1.5, 1 H), 8.14 (d, 1.5, 1 H). Anal. ($C_{15}H_{17}NO_3$) C, H, N. Compounds **10e–g** and **14d** were obtained in a similar manner from **9e**, **9f**, and **9a** (see Table I).

2,2,3-Trimethyl-2*H*-1-benzopyran-6-carbonitrile (12a). Method A. Chromanone **9a** (100 g, 497 mmol), paraformaldehyde (50 g), and piperidine (100 mL, 1.01 mol) were stirred in EtOH (1 L) at 75 °C for 1 h. The solution was cooled to room temperature and treated with $NaBH_4$ (35 g, 925 mmol) in portions, causing violent foaming. The solution was evaporated after 1 h of stirring and the residue was dissolved in CH_2Cl_2 (1.2 L). The solution was washed with dilute HCl and the organic layer dried and evaporated, leaving a crude mixture of diastereomeric alcohols **11a** (125 g) as a brown viscous oil. This was stirred and heated under reflux in dry toluene (700 mL) containing *p*-toluenesulfonic acid (12 g, 70 mmol) for 3 h under a Dean–Stark trap. An additional amount of *p*-toluenesulfonic acid (8 g, 46 mmol) was added and the solution was heated for an additional 3 h. The solution was washed with 10% aqueous NaOH and H_2O and the organic phase was dried and evaporated. The resulting dark oil was subjected to fractional vacuum distillation to give crude **12a** (33 g, 33% overall yield) as a first fraction (0.13 mbar, bp 130–140 °C), which crystallized after standing for some time. The analytical sample of mp 60–61.5 °C was obtained after recrystallization from petroleum ether: NMR (DMSO-d_6) δ 1.42 (s, 6 H), 1.86 (d, 0.7, 3 H), 6.21 (q, 0.7, 1 H), 6.87 (d, 7.8, 1 H), 7.45 (d, 2.0, 1 H), 7.50 (dd, 7.8, 2.0, 1 H). Anal. ($C_{13}H_{13}NO$) C, H, N.

The higher boiling distillation fractions were shown to contain further byproducts, for example, 2,2-dimethyl-3-(1-piperidinylmethyl)-2*H*-1-benzopyran-6-carbonitrile (**12c**), which could be isolated after additional purification steps on a silica gel column. **12c**: mp 116–119 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.44 (s, 6 H), 1.48 (m br, 6 H), 2.39 (m br, 4 H), 2.98 (s br, 2 H), 6.38 (s br, 1 H), 6.90 (d, 7.4, 1 H), 7.54 (dd, 7.4, 1.8, 1 H), 7.56 (d, 1.8, 1 H). Anal. ($C_{18}H_{22}N_2O$) C, H, N. Compounds **12e**, **12f**, and **12g** were prepared in an analogous manner (see Table I) from **9e**, **9f**, and **9a**.

Method B. 4-Hydroxy-3-propanolylbenzonitrile (**17**; 19 g, 108 mmol) and pyrrolidine (3.4 mL, 41 mmol) were refluxed in toluene (100 mL) under a Dean–Stark trap for 2 days. During this time acetone (80 mL, 1.09 mol) was added in portions. The toluene solution was diluted with EtOAc (300 mL) and washed with 1 N HCl and H_2O, and the organic phase dried and evaporated. The residue was chromatographed (silica gel, gradient elution CH_2Cl_2 → EtOAc) to give crystalline 3,4-dihydro-2,2,3-trimethyl-4-oxo-2*H*-1-benzopyran-6-carbonitrile (**14a**; 4 g, 17%) from $(Me_2CH)_2O$: mp 128–130 °C; NMR (DMSO-d_6) δ 1.12 (d, 7.0, 3 H), 1.26 (s, 3 H), 1.50 (s, 3 H), 3.01 (q, 7.0, 1 H), 7.18 (d, 8.1, 1 H), 7.96 (dd, 8.1, 2.1, 1 H), 8.10 (d, 2.1, 1 H). Anal. ($C_{13}H_{13}NO_2$) C, H, N.

Chromanone **14a** was converted to compound **12a** in an analogous manner as described above by $NaBH_4$ reduction and *p*-toluenesulfonic acid treatment with a 68% overall yield. Compounds **14b** and **14h** were converted to **12b** and **12h** (see Table I).

3-[(Benzyloxy)methyl]-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (12d). Compound **12d** was prepared analogously to the procedure described above (method A) from compound **9a** (201.2 g, 1 mol), paraformaldehyde (100 g), piperidine (200 mL, 2.02 mol), and benzyl alcohol (1 L) instead of EtOH. Vacuum distillation of **12a** (60 g, 30%) left a residue that was further purified by Kugelrohr distillation (bath temperature 170–185 °C, 0.13 mbar). The resulting viscous oil (37 g) was chromatographed on silica gel, and the homogeneous fractions were combined and recrystallized from petroleum ether to give **12d** (9.5 g, 3% overall yield): mp 67–69 °C; NMR ($CDCl_3$) δ 1.49 (s, 6 H), 4.10 (d, 0.6, 2 H), 4.57 (s, 2 H), 6.36 (d, 0.6, 1 H), 6.82 (d, 7.6, 1 H), 7.20–7.45 (m, 7 H). Anal. ($C_{20}H_{19}NO_2 \cdot 0.25H_2O$) C, H, N.

3,4-Dihydro-2,2-dimethyl-3-(2-nitroethyl)-4-oxo-2*H*-1-benzopyran-6-carbonitrile (14h). A sodium ethoxide solution was prepared from the reaction of Na (300 mg, 13 mmol) with EtOH (200 mL). Nitromethane (12 g, 197 mmol) was added and stirred for 30 min. After the addition of **10a** (12.6 g, 59 mmol) the reaction mixture was stirred for an additional 12 h and the resulting precipitate of **14h** (9 g, 56%) was collected: mp 185–187 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.29 (s, 3 H), 1.54 (s, 3 H), 2.22 (m, 2 H), 3.03 (dd, 7.4, 4.2, 1 H), 4.59 (m, 1 H), 4.71 (m, 1 H), 7.18 (d, 7.8, 1 H), 7.97 (dd, 7.8, 2.0, 1 H), 8.10 (d, 2.0, 1 H). Anal. ($C_{14}H_{14}N_2O_4$) C, H, N.

3-[(6-Cyano-3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-1-benzopyran-3-yl)methyl]-3,4-dihydro-2,2-dimethyl-3-(methoxymethyl)-4-oxo-2*H*-1-benzopyran-6-carbonitrile (16). Compound **10a** (4.5 g, 21.1 mmol) was added to a sodium methoxide solution prepared from Na (500 mg, 71.7 mmol) with MeOH (150 mL). After stirring overnight at room temperature the forming precipitate of **16** (3.9 g, 81%) was collected: mp 245–247 °C (EtOAc); NMR (DMSO-d_6 + TFA) δ 1.12 (s, 3 H), 1.34 (s, 3 H), 1.55 (s, 3 H), 1.58 (s, 3 H), 1.91 (d, –14.5, 1 H), 2.26 (dd, –14.5, 7.7, 1 H), 2.94 (d, 7.7, 1 H), 3.27 (s, 3 H), 3.38 (d, –11.3, 1 H), 3.84 (d, –11.3, 1 H), 7.07 (d, 9.0, 1 H), 7.12 (d, 9.2, 1 H), 7.74 (d, 1.8, 1 H), 7.84 (dd, 8.8, 1.8, 1 H), 7.90 (dd, 9.0, 1.7, 1 H), 7.92 (d, 1.7, 1 H). Anal. ($C_{27}H_{26}N_2O_5$) C, H, N.

General Procedure for Compounds 15. 3,4-Epoxy-3,4-dihydro-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (15a). 3-Chloroperbenzoic acid (55%, 83 g, 265 mmol) was dissolved in CH_2Cl_2 (400 mL) and the separating H_2O phase was rejected. The organic phase was added dropwise at room temperature to a stirred solution of chromene **12a** (49 g, 246 mmol) in CH_2Cl_2 (250 mL). Stirring was continued overnight and the resulting precipitate was removed. The CH_2Cl_2 was washed with 1 N NaOH, dried, and evaporated, leaving oily epoxide **15a** (51 g, 96%), which crystallized after standing for some time: mp 121–123 °C from $(Me_2CH)_2O$; NMR (DMSO-d_6) δ 1.26 (s, 3 H), 1.49 (s, 3 H), 1.53 (s, 3 H), 3.97 (s, 1 H), 6.92 (d, 9.5, 1 H), 7.70 (dd, 9.5, 1.5, 1 H), 7.98 (d, 1.5, 1 H). Anal. ($C_{13}H_{13}NO_2$) C, H, N.

3-Bromo-3,4-dihydro-4-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (18). NBS (52 g, 292 mmol) was added in portions to a vigorously stirred solution of chromene **12a** (60 g, 301 mmol) in DMSO (80 mL) and H_2O (5.3 mL, 294 mmol) while the temperature was maintained at below 70 °C. After the exothermic reaction, stirring was continued for an additional 3 h, followed by pouring into H_2O and extraction with CH_2Cl_2. Purification was achieved by chromatography on silica gel with petroleum ether/CH_2Cl_2 mixtures using a gradient elution technique. The most polar fractions were combined to give compound **18** (50 g, 56%): mp 87–91 °C after recrystallization from $(Me_2CH)_2O$; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.67 (s, 3 H), 1.69 (s, 3 H), 2.72 (s br, 1 H), 5.21 (s, 1 H), 6.85 (d, 8.1, 1 H), 7.49 (dd, 8.1, 1.8, 1 H), 7.85 (d, 1.8, 1 H). Anal. ($C_{13}H_{14}BrNO_2$) C, H, Br, N.

(3*S*,4*S*)-(–)-3,4-Epoxy-3,4-dihydro-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (15i). With stirring at room temperature in pyridine (300 mL), compound **18** (30 g, 101 mmol) was treated with (1*R*)-(+)-camphanic acid chloride[24] (25.5 g, 118 mmol) and 4-(dimethylamino)pyridine (200 mg, 1.64 mmol) for 12 h. After evaporation, the residue was taken up in CH_2Cl_2 and washed with 1 N HCl. The organic phase was evaporated and the resulting oil gave, on recrystallization with $(Me_2CH)_2O$, a mixture (HPLC 70:30) of the diastereomeric camphanates (28 g). This was subjected to repeated fractional crystallization from $(Me_2CH)_2O$ to yield 8.9 g (20%) of the nonpolar, substantially pure (3*S*,4*S*)-3-bromo-6-cyano-3,4-dihydro-2,2,3-trimethyl-4-chromanyl (1*R*)-camphanate; mp 158–160 °C.

A solution of the foregoing camphanate (8.7 g, 18.3 mmol) in dioxane (70 mL) and 1 N NaOH (40 mL) was stirred at room temperature for 3.5 h. Evaporation of the solution gave a residue,

(24) Gerlach, H. Determination of the Chirality Sense of the Enantiomeric 2,6-Adamantanediols. *Helv. Chim. Acta* **1985**, *68*, 1815–1821.

which was taken up with CH_2Cl_2, washed with H_2O, and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a solid (3.8 g, 97%), a portion of which was recrystallized from $(Me_2CH)_2O$ to give **15i**: mp 153–155 °C; $[\alpha]^{20}_D$ (*c* 1, MeOH) −134.1°. Anal. ($C_{13}H_{13}NO_2$) C, H, N. With (1*S*)-(−)-camphanic acid chloride the (3*R*,4*R*)-(+)-epoxide **15j** was prepared in an analogous manner: $[\alpha]^{20}_D$ (*c* 1, MeOH) +135.2° (see Table I).

Resolution of 15i and 15j by Entrainment. Epoxide **15a** (50 g) was dissolved in THF (120 mL) with warming, filtered, and placed in a thermostatic reaction vessel. At a low stirring rate, finely ground enantiomer **15i** (0.1 g) was added at 25 °C. The temperature was lowered to 21 °C during 2 h in the course of which crystallization took place. The crystals (2 g) so obtained were found to be substantially pure **15i** after recrystallization from *tert*-butyl methyl ether; mp 153–155 °C. A further amount of **15a** (1.9 g) was added to the mother liquor (120 mL), dissolved with warming, and filtered. Enantiomer **15j** (2.5 g) resulted from a crystallization which was carried out as described in the previous experiment after entrainment with **15j** (0.1 g): mp 153–155 °C (*tert*-butyl methyl ether). Subsequently, **15i** was crystallized again applying the same procedure, etc. With maintenance of constant solid/liquid proportions, the yields per crystallization step after several cycles was increased to 3.5 g.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (19a) and *trans*-3,4-Dihydro-3-hydroxy-2,2,3-trimethyl-4-(2-pyridyloxy)-2*H*-1-benzopyran-6-carbonitrile (20).** Epoxide **15a** (19.4 g, 90.1 mmol) and 2-pyridinol (9.3 g, 97.8 mmol) were heated under reflux in EtOH (250 mL) containing pyridine (9 mL, 112 mmol) for 7 days. Evaporation of the reaction mixture gave a residue which was chromatographed on silica gel, using petroleum ether/CH_2Cl_2/EtOAc mixtures in a gradient elution. The nonpolar component, compound **20** (9.5 g, 34%), was recrystallized from $(Me_2CH)_2O$: mp 105–107 °C; NMR (DMSO-d_6) δ 1.23 (s, 3 H), 1.40 (s, 3 H), 1.47 (s, 3 H), 5.45 (s, 1 H), 6.38 (s, 1 H), 6.96 (d, 8.2, 1 H), 6.98 (d, 8, 1 H), 7.10 (dd, 7, 5, 1 H), 7.55 (d, 1.7, 1 H), 7.65 (dd, 8.4, 1.7, 1 H), 7.81 (ddd, 7.8, 7.3, 1.8, 1 H), 8.28 (dd, 5.2, 1.8, 1 H). Anal. ($C_{18}H_{19}N_2O_3$) C, H, N. The polar component, compound **19a** (8.5 g, 30%), was recrystallized from EtOAc: mp 185–186 °C; NMR data of the main component (DMSO-d_6) δ 1.04 (s, 3 H), 1.37 (s, 3 H), 1.44 (s, 3 H), 5.25 (s br, 1 H), 6.24 (m, 1 H), 6.55 (d, 8.6, 1 H), 6.59 (s, 1 H), 7.05 (d, 7.8, 1 H), 7.14 (s br, 1 H), 7.18 (dd, 6.8, 1.4, 1 H), 7.50 (ddd, 8.1, 6.7, 1.4, 1 H), 7.68 (dd, 8.8, 1.4, 1 H). Anal. ($C_{18}H_{19}N_2O_3$) C, H, N. Similar treatment of **15e** and **15f** yielded compounds **19b** and **19c**.

4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (21). Chromanol **19a** (1.5 g, 4.8 mmol) and NaOH on a carrier (0.8–1.6 mm, ~14–25 mesh ASTM, Cat. No. 1567, E. Merck; 1.5 g) were heated under reflux in dioxane (50 mL) for 20 min. The reaction mixture was cooled, filtered, and evaporated, and the crude residue recrystallized from Me_2CHOH to give 900 mg (64%) of compound **21**: mp 210–212 °C; NMR (DMSO-d_6) δ 1.53 (s, 6 H), 1.61 (s, 3 H), 6.38 (m, 1 H), 6.54 (d, 8.8, 1 H), 6.73 (d, 1.8, 1 H), 7.03 (d, 7.4, 1 H), 7.46 (dd, 6.7, 1.4, 1 H), 7.59 (m, 1 H), 7.62 (m, 1 H). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

***trans*-3,4-Epoxy-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (22).** 3-Chloroperbenzoic acid (70%, 16 g, 65 mmol) was dissolved in CH_2Cl_2 (100 mL), and the separating H_2O phase was rejected. Chromene **21** (10 g, 34 mmol) was added to the CH_2Cl_2, and the mixture was stirred for 3 days at room temperature. The solution was filtered, washed with 1 N NaOH, dried, and evaporated. The residue was purified by chromatography on silica gel with CH_2Cl_2/20% EtOAc to give epoxide **22** (5 g, 47%): mp 176–178 °C (Et_2O); NMR (DMSO-d_6) δ 1.24 (s, 3 H), 1.47 (s, 3 H), 1.58 (s, 3 H), 6.50 (m, 2 H), 7.08 (m, 2 H), 7.65 (m, 2 H), 7.79 (dd, 8.1, 2.1, 1 H). Anal. ($C_{18}H_{16}N_2O_3 \cdot 0.25H_2O$) C, H, N.

3,4-Dihydro-2,2,3-trimethyl-4-oxo-3-(2-pyridyloxy)-2*H*-1-benzopyran-6-carbonitrile (23). Epoxide **22** (610 mg, 1.95 mmol) was dissolved in EtOH (20 mL) and saturated with gaseous NH_3. The solution was heated in a sealed bomb tube at 110 °C overnight. Crystals of compound **23** (500 mg, 82%) separated from the cooled solution: mp 205–207 °C; NMR (DMSO-d_6) δ 1.28 (s, 3 H), 1.52 (s, 3 H), 1.70 (s, 3 H), 6.76 (d, 7.8, 1 H), 6.95 (dd, 6.7, 4.6, 1 H), 7.10 (d, 8.1, 1 H), 7.65 (ddd, 8.5, 7.4, 2.1, 1 H), 7.85 (dd, 8.2, 2.1, 1 H), 7.98 (m, 2 H). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

***trans*-4-Amino-3,4-dihydro-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (24).** Gaseous NH_3 was bubbled into a boiling solution of epoxide **15a** (4.3 g, 20 mmol) in EtOH (50 mL) for 24 h. The crude product obtained on evaporation of the solvent was triturated with $(Me_2CH)_2O$ to give compound **24** (3.3 g, 71%): mp 132–134 °C (Et_2O/Me_2CHOH); NMR (DMSO-d_6 + TFA) δ 1.09 (s, 3 H), 1.29 (s, 3 H), 1.45 (s, 3 H), 4.46 (s br, 1 H), 7.02 (d, 8.1, 1 H), 7.23 (dd, 8.1, 1.5, 1 H), 7.92 (d, 1.5, 1 H). Anal. ($C_{13}H_{16}N_2O_2$) C, H, N.

***trans*-4-(4-Chlorobutyramido)-3,4-dihydro-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (25).** Compound **24** (2.8 g, 12 mmol) and NaOH pellets (500 mg, 12.5 mmol) were stirred in $CHCl_3$ (30 mL) and H_2O (30 mL), and 4-chlorobutyryl chloride (1.4 mL, 12.5 mmol) was added to the solution at room temperature. The layers were separated after stirring overnight, and the organic phase was washed with H_2O, dried, and evaporated to give compound **25** (3.3 g, 81%) after recrystallization from Me_2CHOH: mp 143–145 °C; NMR (DMSO-d_6) δ 1.04 (s, 3 H), 1.30 (s, 3 H), 1.39 (s, 3 H), 2.08 (m, 2 H), 2.5 (m, 2 H), 3.73 (t, 6.7, 2 H), 5.03 (s br, 1 H), 5.21 (d, 8.8, 1 H), 6.92 (d, 8.8, 1 H), 7.47 (d, 1.5, 1 H), 7.60 (dd, 8.8, 1.5, 1 H), 8.11 (d, 8.8, 1 H). Anal. ($C_{17}H_{21}ClN_2O_3$) C, H, Cl, N.

***trans*-3,4-Dihydro-3-hydroxy-2,2,3-trimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (26).** Compound **25** (2.3 g, 6.8 mmol), anhydrous K_2CO_3 (20 g, 145 mmol), and KI (2 g, 12 mmol) in Me_2CO (250 mL) were stirred and heated under reflux for 18 h. The reaction mixture was cooled and filtered, and the crude residue recrystallized from Me_2CHOH to give compound **26** (1.5 g, 71%): mp 195–197 °C; NMR (DMSO-d_6) δ 1.10 (s, 3 H), 1.30 (s, 3 H), 1.38 (s, 3 H), 2.02 (m, 2 H), 2.40 (m, 2 H), 3.25 (m, 2 H), 5.14 (s br, 1 H), 5.45 (s br, 1 H), 6.96 (d br, 7.8, 1 H), 7.40 (s br, 1 H), 7.60 (d br, 7.8, 1 H). Anal. ($C_{17}H_{20}N_2O_3 \cdot 0.5H_2O$) C, H, N.

2,2,3-Trimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (27). NaH (80%, 1 g, 33.3 mmol) was added in portions to a vigorously stirred solution of epoxide **15a** (6.4 g, 27.7 mmol) and 2-pyrrolidone (3 g, 35.2 mmol) in DMSO (50 mL) under N_2. The reaction mixture was stirred for 4 h at room temperature, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried, filtered, and evaporated, leaving a residue which was recrystallized from EtOAc to give compound **27** (4.2 g, 50%): mp 184–186 °C; NMR (DMSO-d_6) δ 1.43 (s, 3 H), 1.47 (s, 3 H), 1.72 (s, 3 H), 2.03–2.65 (m, 4 H), 3.49 (m, 2 H), 6.95 (d, 7.8, 1 H), 7.34 (d, 1.8, 1 H), 7.58 (dd, 7.8, 1.8, 1 H). Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

***trans*-3,4-Dihydro-4-[(1,2-dihydro-2-oxo-1-pyridyl)-amino]-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (29).** Epoxide **15a** (3.15 g, 14.6 mmol) and 1-amino-1,2-dihydropyridin-2-one[16] (1.1 g, 10 mmol) were melted together in a small tube with stirring at 190 °C for 8 h. The resulting dark gum was chromatographed on silica gel (CH_2Cl_2 → EtOAc). Chromatographically homogeneous fractions (500 mg, 15%) were combined, and a portion was recrystallized from Me_2CHOH to give compound **29**: mp 184–187 °C; NMR (DMSO-d_6) δ 1.24 (s, 3 H), 1.28 (s, 3 H), 1.43 (s, 3 H), 4.22 (d, 3.9, 1 H), 5.21 (s, 1 H), 6.25 (td, 6.7, 1.1, 1 H), 6.54 (dd, 8.8, 1.3, 1 H), 6.89 (d, 8.4, 1 H), 6.90 (d, 3.8, 1 H), 7.47 (m, 1 H), 7.62 (dd, 8.4, 1.3, 1 H), 7.95 (dd, 7, 1.4, 1 H), 8.36 (d, 1.3, 1 H). Anal. ($C_{18}H_{19}N_3O_3$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-4-[(3-oxo-1-cyclopent-1-enyl)oxy]-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (30).** 1,3-Cyclopentanedione (4.2 g, 42.8 mmol) was dissolved in dry THF (250 mL) under N_2, and NaH (80%; 1.3 g, 43.3 mmol) was added. After 45 min of stirring at room temperature epoxide **15a** (9.2 g, 42.7 mmol), dissolved in THF (75 mL) and $BF_3 \cdot Et_2O$ (4.8 mL, 38.2 mmol), was added onto the reaction solution. After 12 h the reaction solution was poured on a diluted $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the residue was chromatographed on silica gel (EtOAc/1% MeOH) to give compound **30** (3.2 g, 24%): mp 204–206 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.17 (s, 3 H), 1.37 (s, 3 H), 1.40 (s, 3 H), 2.39 (m, 2 H), 2.58–2.94 (m, 2 H), 5.34 (s, 1 H), 5.43 (s, 1 H), 5.83 (s, 1 H), 6.98 (d, 9.2, 1 H), 7.67 (m, 2 H). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

(-)-(3*S*,4*R*)-3,4-Dihydro-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy]-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (32a). Epoxide **15i** (6.3 g, 29.3 mmol), 3,6-pyridazinediol (3.3 g, 29.4 mmol), and pyridine (3 mL, 37.2 mmol) were refluxed in EtOH (150 mL) for 7 days. The solution was evaporated and the residue chromatographed on silica gel (EtOAc/1% MeOH). The homogeneous fractions were combined, crystallized from EtOAc, and cautiously vacuum-dried up to 100 °C to give 8.6 g (86%) of compound **32a**: mp 135 °C; $[\alpha]^{20}_D$ (*c* 1, MeOH) -232.0°; NMR (DMSO-d_6) δ 1.20 (s, 3 H), 1.35 (s, 3 H), 1.43 (s, 3 H), 5.38 (s, 1 H), 5.88 (s, 1 H), 6.94 (d, 10.2, 1 H), 6.95 (d, 7.5, 1 H), 7.25 (d, 10.2, 1 H), 7.64 (dd, 7.5, 1.5, 1 H), 7.68 (d, 1.4, 1 H), 12.21 (s br, 1 H). Anal. ($C_{17}H_{17}N_3O_4 \cdot 0.25H_2O$) C, H, N. The dextrorotatory enantiomer **32j** was prepared analogously from epoxide **15j**. Similar treatment of epoxides **15e**, **15f**, and **15b** furnished racemic compounds **32b**, **32c**, and **32f**, and treatment of **15a** with **33a** yielded compound **34** (see Table II).

***trans*-3-Benzyl-3,4-dihydro-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy]-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (32d).** Epoxide **15g** (2 g, 6.8 mmol), 3,6-pyridazinedione (1 g, 8.9 mmol), pyridine (1 mL, 12.4 mmol), and EtOH (40 mL) were heated in a bomb tube at 230 °C for 20 h. After cooling, the precipitate was removed and the solution evaporated and chromatographed on silica gel (CH_2Cl_2 → EtOAc). The polar fractions were combined, and the most polar compound **32d** (60 mg, 2.2%) was isolated by a further chromatography on a LiChrosorb Si 60 steel column (E. Merck, Cat. No. 9387): mp 242–243 °C (Et_2O); NMR ($CDCl_3$ + DMSO-d_6) δ 1.57 (s, 3 H), 1.64 (s, 3 H), 2.10 (s, 1 H), 2.99 (d, -13.8, 1 H), 3.10 (d, -13.8, 1 H), 5.61 (s, 1 H), 6.77–6.96 (m, 3 H), 7.16 (s, 5 H), 7.49 (dd, 8.8, 1.7, 1 H), 7.79 (d, 1.7, 1 H), 11.00 (s br, 1 H). Anal. ($C_{23}H_{21}N_3O_4$) C, H, N.

***trans*-3,4-Dihydro-4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)oxy]-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (32e).** Compound **32a** (racemate; 1 g, 3.1 mmol), dimethyl sulfate (2 mL, 21.1 mmol), and anhydrous K_2CO_3 (3 g, 21.8 mmol) in Me_2CO (40 mL) were stirred and heated under reflux for 2 h. The reaction mixture was cooled, filtered, and evaporated, and the residue taken up in H_2O and extracted with EtOAc. After drying, filtration, and evaporation of the organic phase, compound **32e** (900 mg, 86%) was crystallized from Et_2O/EtOAc: mp 197–199 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.21 (s, 3 H), 1.37 (s, 3 H), 1.47 (s, 3 H), 3.58 (s, 3 H), 5.39 (s, 1 H), 5.92 (s, 1 H), 6.96 (d, 8.1, 1 H), 7.01 (d, 9.9, 1 H), 7.27 (d, 9.9, 1 H), 7.67 (dd, 8.1, 1.3, 1 H), 7.72 (d, 1.3, 1 H). Anal. ($C_{18}H_{18}N_3O_4$) C, H, N. Compound **32g** was prepared in a similar manner with diethyl sulfate.

***trans*-3,4-Dihydro-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)-oxy]-3-hydroxy-3-(hydroxymethyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (32i).** Benzyl compound **32h** (2.5 g, 5.8 mmol) and ammonium formate (1.5 g, 23.8 mmol) were stirred and heated under reflux in MeOH (100 mL) containing Pd/C (10%, 2.5 g) for 6 h. The catalyst was removed, the solution evaporated, and the residue chromatographed on silica gel, by using EtOAc/MeOH mixtures in a gradient elution. The chromatographically homogeneous polar fractions were combined and triturated with Et_2O to give compound **32i** (400 mg, 20%): mp 212–215 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.38 (s, 3 H), 1.44 (s, 3 H), 3.53 (dd, -11, 4.2, 1 H), 3.76 (dd, -11, 6.3, 1 H), 4.77 (m, 1 H), 5.09 (s, 1 H), 5.86 (s, 1 H), 6.89 (d, 10.2, 1 H), 6.95 (d, 8.5, 1 H), 7.14 (d, 10.1, 1 H), 7.65 (dd, 8.5, 1.5, 1 H), 7.93 (d, 1.7, 1 H), 12.25 (s br, 1 H). Anal. ($C_{17}H_{17}N_3O_5$) C, H; N: calcd, 12.24; found 11.49.

3-Amino-1-methyl-1,6-dihydropyridazin-6-one (33b). 3-Amino-6-pyridazinol[18] (500 mg, 4.5 mmol), NaOH pellets (180 mg, 4.5 mmol), and MeI (0.28 mL, 4.5 mmol) were refluxed in dry EtOH (20 mL) for 2.5 h. The solution was evaporated and the residue digested by hot EtOAc (250 mL) and filtered. The EtOAc was evaporated and the residue crystallized from MeOH to give compound **33b** (160 mg, 28%): mp 220–223 °C; NMR (DMSO-d_6) δ 3.40 (s, 3 H), 5.74 (s br, 2 H), 6.72 (d, 9.9, 1 H), 6.95 (d, 9.9, 1 H). Anal. ($C_5H_7N_3O$) C, H, N.

***trans*-3,4-Dihydro-4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)amino]-3-hydroxy-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (35).** Compound **33b** (500 mg, 4 mmol) was treated with NaH (80%; 120 mg, 4 mmol) and epoxide **15a** (1 g, 4.6 mmol) in DMSO (25 mL), with stirring, at room temperature for 4 h. The solution was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated. The crude residue was purified by chromatography on a Lobar prepacked column, size C, LiChroprep Si 60, 40–63 μm (E. Merck), with gradient elution (EtOAc → EtOAc/5% MeOH) to give compound **35** (160 mg, 20%): mp 258–260 °C (EtOAc); NMR (DMSO-d_6) δ 1.09 (s, 3 H), 1.35 (s, 3 H), 1.41 (s, 3 H), 3.45 (s, 3 H), 5.10 (s br, 1 H), 5.15 (d, 9.5, 1 H), 6.63 (d, 9.5, 1 H), 6.82 (d, 10.2, 1 H), 6.92 (d, 8.1, 1 H), 7.23 (d, 10.2, 1 H), 7.53 (d, 1, 1 H), 7.60 (dd, 8.1, 1, 1 H). Anal. ($C_{18}H_{20}N_4O_3$) C, H, N.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2,3-trimethyl-2*H*-1-benzopyran-6-carbonitrile (36).** To a cold (-70 °C) solution of compound **3**[5] (2 g, 7.2 mmol) in dry THF (50 mL) MeLi in Et_2O (5%; 4.5 mL, 7.2 mmol) was slowly added by syringe under N_2. The resultant brown solution that was stirred at low temperature for 30 min turned yellow on quenching with MeOH (20 mL). The reaction mixture was evaporated and the residue purified on a silica gel column (Et_2O) to give compound **36** (680 mg, 32%): mp 182–185 °C; NMR (DMSO-d_6, 120 °C) δ 0.86 (d, 7.5, 3 H), 1.26 (s, 3 H), 1.48 (s, 3 H), 2.5 (br, 1 H), 5.82 (br, 1 H), 6.21 (td, 6.6, 0.5, 1 H), 6.47 (d br, 8.8, 1 H), 6.92 (m, 2 H), 7.28 (d br, 7.5, 1 H), 7.41 (m, 1 H), 7.51 (dd, 8.8, 1.8, 1 H). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

Influence on Membrane Potential of Vascular Smooth Muscle Cells. Experiments were carried out on strips of rabbit main pulmonary artery. Changes of membrane potential were recorded with intracellular glass microelectrodes and conventional recording equipment. After an equilibration period of 60 min, the membrane potential of several cells was measured and taken as an indication of the quality of the preparation. The membrane potential reached after addition of 1 μM noradrenaline was taken as the baseline value. The effects of test compounds were examined by exchanging the medium of the bath with solutions containing increasing concentrations of the compounds. The membrane potential of at least four cells was determined per concentration. The maximal increase (ΔmV) in membrane potential hyperpolarization recorded up to a concentration of 100 μM was taken as an indication for the efficacy of a compound.

Relaxing and Antispasmodic Activity in Isolated Blood Vessels: General Preparation. Blood vessels were removed from animals and mounted in 50-mL organ baths containing physiological salt solution (PSS) of the following composition (in mM): NaCl, 114.1; KCl, 4.7; $MgSO_4$, 1.2; $CaCl_2$, 1.9; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11.1. The bathing solution was maintained at 37 °C and aerated with a mixture of 95% O_2/5% CO_2. Resting tensions of 2 g were applied to the tissues. The rings were allowed to equilibrate for 60–90 min. Tissue responses were measured with isometric force displacement transducers and were recorded on a suitable recorder.

Coronary Artery. Pig hearts were obtained from a commercial slaughter house and transferred to the laboratory in aerated PSS. The left arteria descendens (LAD) was excised and placed in warmed PSS. The blood vessels were dissected free from fat and connective tissue and cut into rings ca. 5 mm wide. Coronary arteries were contracted with 0.3–1 μM acetylcholine; these concentrations induced ca. 80% of the maximal response to acetylcholine. After equilibration, control contractility to a given agonist was established as follows: Acetylcholine was added to the bath, and the contractile response was recorded until a stable value was obtained; the preparation was then washed three times and the tension allowed to return to baseline. This procedure was repeated every 45 min for a total of three or four cycles. The level of the contraction observed during the last cycle was used as the control (predrug) value. Subsequent contractions were obtained in the presence of increasing concentrations of the test compound which was added 30 min prior to the agonist. One vessel ring from each animal was exposed to the solvent without test compound and served as time and solvent control. The reduction in contractile force in the presence of the test compound was expressed as a percentage of the predrug value.

Rabbit Main Pulmonary Artery. Rabbits were stunned by a blow on the head and exsanguinated. The main pulmonary artery was excised and placed in PSS. The blood vessels were dissected free from fat and connective tissue and cut into rings

ca. 5 mm wide. Rings were contracted with 0.7–1 μM noradrenaline; this concentration induced ca. 80% of the maximal response to the agonist. After force had reached a stable value, concentration/response curves were obtained for the test compound by increasing the concentration of the compound in increments of 0.5 log units. The next higher concentration was added after previous force had reached a stable value. One vessel ring from each animal was exposed to the solvent without test compound and served as time and solvent control. The reduction in contractile force in the presence of the test compound was expressed as a percentage of the predrug value.

Evaluation of Results. The results were expressed as mean values ± SEM. IC_{50} values (concentrations required to inhibit predrug responses by 50%) were determined graphically for each experiment and are given as geometric means with 95% confidence limits.

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Registry No. (±)-**2**, 123595-75-5; **3**, 117545-11-6; (±)-**6**, 129421-71-2; **9a**, 121021-88-3; **9e**, 111478-49-0; **9f**, 121021-84-9; **10a**, 126920-51-2; **10e**, 135800-05-4; **10f**, 135800-06-5; **10g**, 135800-07-6; (±)-*cis*-**11a**, 135799-83-6; (±)-*trans*-**11a**, 135800-33-8; **12a**, 126920-53-4; **12b**, 135800-09-8; **12c**, 135800-08-7; **12d**, 135800-11-2; **12e**, 135800-12-3; **12f**, 135800-13-4; **12g**, 135800-14-5; **12h**, 135800-15-6; (±)-**13**, 135799-84-7; (±)-**14a**, 135799-85-8; (±)-**14b**, 135800-17-8; (±)-**14c**, 135800-18-9; (±)-**14d**, 135800-19-0; (±)-**14h**, 135800-20-3; (±)-**15a**, 135799-86-9; (±)-**15b**, 135800-21-4; (±)-**15d**, 135800-04-3; (±)-**15e**, 135800-22-5; (±)-**15f**, 135800-23-6; (±)-**15g**, 135800-10-1; (±)-**15h**, 135800-16-7; **15i**, 135836-40-7; **15j**, 135836-41-8; (±)-**16**, 135799-87-0; **17**, 70978-58-4; (±)-**18**, 135799-88-1; (3*S*,4*S*)-**18** (1*R*)-camphanate, 135800-34-9; (3*R*,4*R*)-**18** (1*R*)-camphanate, 135910-79-1; (±)-**19a**, 135799-89-2; (±)-**19b**, 135800-24-7; (±)-**19c**, 135800-25-8; (±)-**20**, 135799-90-5; **21**, 126920-29-4; (±)-**22**, 135799-91-6; (±)-**23**, 135799-92-7; (±)-**24**, 135799-93-8; (±)-**25**, 135799-94-9; (±)-**26**, 135799-95-0; **27**, 126920-35-2; (±)-**28**, 135799-96-1; (±)-**29**, 135799-97-2; (±)-**30**, 135799-98-3; (±)-**31**, 135799-99-4; **32a**, 135800-00-9; (±)-**32a**, 135910-77-9; (±)-**32a**·0.5EtOAc, 135910-78-0; (±)-**32b**, 135800-26-9; (±)-**32c**, 135800-27-0; (±)-**32d**, 135800-28-1; (±)-**32e**, 135800-29-2; (±)-**32f**, 135800-30-5; (±)-**32g**, 135800-36-1; (±)-**32h**, 135800-31-6; (±)-**32i**, 135800-32-7; **32j**, 135800-35-0; **33a**, 57041-95-9; **33b**, 13506-28-0; (±)-**34**, 135800-01-0; (±)-**35**, 135800-02-1; (±)-**36**, 135800-03-2; nitromethane, 75-52-5; (1*R*)-(+)-camphanic acid chloride, 104530-16-7; (1*S*)-(−)-camphanic acid chloride, 39637-74-6; 2-pyridinol, 142-08-5; 1-amino-1,2-dihydropyridin-2-one, 54931-11-2; 4-chlorobutyryl chloride, 4635-59-0; 2-pyrrolidone, 616-45-5; 1,3-cyclopentanedione, 3859-41-4; 3,6-pyridazinedione, 42413-70-7.

Supplementary Material Available: X-ray crystallographic data, including positional parameters, bond distances, bond angles, and anisotropic displacement parameter expressions, for **2**, **3**, **6**, **19a**, **32a**, and **36** (43 pages). Ordering information is given on any current masthead page.

Separation of α_1 Adrenergic and *N*-Methyl-D-aspartate Antagonist Activity in a Series of Ifenprodil Compounds

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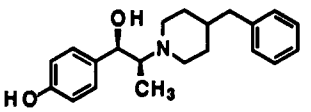
Ifenprodil (1) represents a new class of *N*-methyl-D-aspartate (NMDA) antagonist. This drug also possesses potent activity at several other brain receptors (most notably α_1 adrenergic receptors). We have prepared the enantiomers and diastereomers of ifenprodil along with a series of partial structures in order to explore the basic structure activity relations within this class of compounds. From this study, it is clear that α_1 adrenergic and NMDA receptor activities may be separated by selection of the threo relative stereochemistry. Examination of the optical isomers of *threo*-ifenprodil (2) reveals that no further improvement in receptor selectivity is gained from either antipode. Individual removal of most of the structural fragments from the ifenprodil molecule generally results in less active compounds although fluorinated derivative 9 with threo relative stereochemistry is somewhat more potent and substantially more selective for the NMDA receptor. Finally a minimum structure for activity in this series (14) has been identified. This stripped-down version of ifenprodil possesses nearly equivalent affinity for the NMDA receptor with no selectivity over α_1 adrenergic receptors.

Introduction

Since the surprising discovery that the commercial antihypertensive agent ifenprodil (1) possessed *N*-methyl-D-aspartate (NMDA) antagonist activity,[1] considerable attention has been directed toward elucidating its mechanism of action. Ifenprodil is structurally unrelated to any of the known classes of NMDA antagonists[2] and does not interact directly through these known sites of action. Currently, it is postulated that ifenprodil exerts its antagonist effects at an allosteric polyamine site which positively modulates the NMDA receptor, although this point is controversial.[3]



Ifenprodil (1)

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