Synthesis and Antihypertensive Activity of 4-(Substituted-carbonylamino)-2*H*-1-benzopyrans

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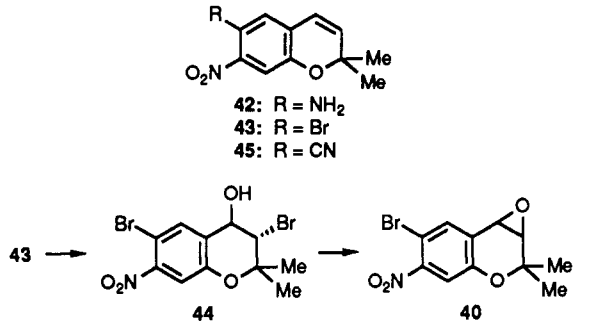
Received February 7, 1990

The synthesis and antihypertensive activity of a series of novel 4-(substituted-carbonylamino)-2*H*-1-benzopyran-3-ols, administered orally to conscious spontaneously hypertensive rats, are described. Optimum activity was observed for compounds with alkyl, amino, or aryl groups flanking the carbonyl group. Of the alkyl and amino series the most potent compounds contained the methyl and methylamino groups, respectively. Several analogues have been compared with cromakalim (1) for their effects on potassium ion efflux in the rabbit mesenteric artery using rubidium-86 as a marker. The ability of each compound to enhance rubidium-86 efflux is approximately parallelled by its blood pressure lowering activity, and thus these analogues, like compound (1), belong to the series of drugs which have been classified as potassium-channel activators.

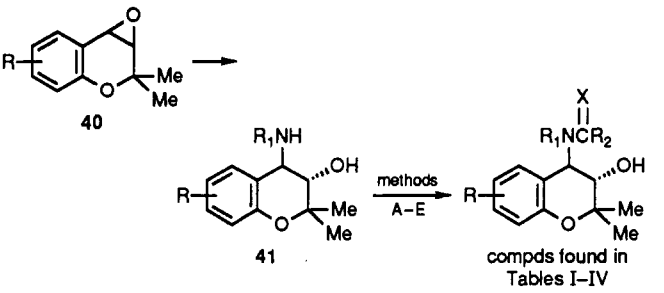
Recently, we have described[1] a novel group of antihypertensive agents, the 4-(cyclic-amido)-2*H*-1-benzopyran-3-ols, which are the forerunners of an important new family of drugs classified as potassium-channel activators. Such compounds have been shown to hyperpolarize the membrane potential of vascular smooth muscle cells,[2] a phenomenon which is due to enhanced efflux of intracellular potassium ions.[3] It is considered that the net effect of this process is to relax blood vessels and thereby to reduce blood pressure in the intact animal.[4]

Our previous work[1] culminated in (±)-*trans*-6-cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-ol (1, cromakalim, see Table I) being progressed to clinical investigation. That work[1] also described certain of the molecular characteristics necessary for optimum activity, among which was the presence of a cyclic amido substituent at C(4) of tightly defined size, optionally substituted regioselectively by a heteroatom. We were interested in preparing acyclic analogues of these compounds to compare activities with their cyclic counterparts, since it had been observed[5] that, in the previous 4-amino-2*H*-1-benzopyran-3-ol series, a cyclic amino substituent such as pyrrolidine conferred significantly more activity (about 30-fold) in the deoxycorticosterone acetate (DOCA)/saline treated hypertensive rat than the related acyclic diethylamino group. Surprisingly, the acyclic analogue of compound 1 (the *N*-acetylethylamino compound 2; see Table I) possessed good antihypertensive activity in the spontaneously hypertensive rat (SHR), being approximately 3-fold less potent than compound 1. This activity is likely, therefore, to be due to the presence of the carbonyl group, and it prompted the synthesis of a series of carbonyl-containing derivatives of various 4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols and their evaluation in the SHR. Studies on the mechanism of action of the cyclic analogue 1, involving enhanced efflux of intracellular potassium ions,[3] were extended to certain of these analogues by using the rabbit isolated mesenteric artery preparation. Pinacidil, which has recently been shown[6] to enhance the outward movement of potassium ions through smooth muscle membranes, was included for comparison in both pharmacological screens.

Scheme I



Scheme II



Chemistry. Convenient starting materials for the synthesis of the compounds described in Tables I–IV are (±)-3,4-epoxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans (**40**), the syntheses of which have been described before.[1,5,7] The exception was the novel epoxide **40** (R = 6-Br, 7-NO_2; Scheme I). Thus, reaction of the diazonium salt of 6-amino-7-nitrobenzopyran **42** with copper(I) bromide gave 6-bromo-7-nitrobenzopyran **43**, which on treatment with *N*-bromosuccinimide yielded bromohydrin **44**. The usual reaction with potassium hydroxide gave epoxide **40** (R = 6-Br, 7-NO_2). It is noteworthy that introduction of a 6-cyano substituent at the initial stage was thwarted by the failure of 6-cyano-7-nitrobenzopyran **45** to form the appropriate bromohydrin.

Benzopyran epoxides **40** were converted to *trans*-4-aminobenzopyran-3-ols **41** (Scheme II) by treatment with amines (R_1NH_2), and the amino alcohols were then con-

(1) 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.
(2) Hamilton, T. C.; Weir, S. W.; Weston, A. H. *Br. J. Pharmacol.* **1986**, *88*, 103.
(3) Coldwell, M. C.; Howlett, D. R. *Biochem. Pharmacol.* **1987**, *36*, 3663.
(4) Buckingham, R. E.; Clapham, J. C.; Hamilton, T. C.; Longman, S. D.; Norton, J.; Poyser, R. H. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 798.
(5) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1983**, *26*, 1582.
(6) Bray, K. M.; Newgreen, D. T.; Small, R. C.; Southerton, J. S.; Taylor, S. G.; Weir, S. W.; Weston, A. H. *Br. J. Pharmacol.* **1987**, *91*, 421.
(7) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Showell, G. A. *J. Med. Chem.* **1984**, *27*, 1127.

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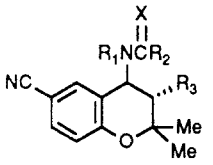
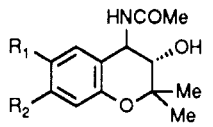
Table I. *trans*-4-(Substituted-alkylamido)-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols and Analogues



compd	R_1	R_2	R_3	X	method[a]	% yield	mp, °C	recryst[b] solvent	formula	anal.[c]	dose, mg/kg po	max fall[d] in BP, % ± SEM
1[e]	$-(CH_2)_3-$		OH	O							0.1	13 ± 5
											0.3	39 ± 11
											1.0	47 ± 1
2	Et	Me	OH	O	B	42	168–170	E	$C_{16}H_{20}N_2O_3$	C, H, N	0.3	14 ± 2
											1.0	22 ± 5
3	Me	Me	OH	O	B	25	197–198	E	$C_{15}H_{18}N_2O_3$	C, H, N	0.3	11 ± 1
											1.0	31 ± 4
4	$(CH_2)_2Me$	Me	OH	O	A	79	193–195	E–P	$C_{17}H_{22}N_2O_3$	C, H, N	1.0	24 ± 3
											3.0	58 ± 2
5	H	Me	OH	O	B	17	203–205	E	$C_{14}H_{16}N_2O_3$	C, H, N	0.1	18 ± 2
											0.3	47 ± 5
											1.0	67 ± 4
6	H	H	OH	O	C	10	228.5–230.5	E	$C_{13}H_{14}N_2O_3$	C, H, N	1.0	10 ± 2
											10.0	26 ± 3
7	H	Et	OH	O	A	25	115–117	E	$C_{15}H_{18}N_2O_3$	C, H; N[f]	0.3	10 ± 3
											1.0	29 ± 4
8	H	$(CH_2)_3Me$	OH	O	A	34	158–159	E–P	$C_{17}H_{22}N_2O_3$	C, H, N	3.0	18 ± 6
											10.0	64 ± 4
9	H	Me	OH	S	*a*	15	176–180	H	$C_{14}H_{16}N_2O_2S$	C, H; N, S[g]	0.3	26 ± 6
											1.0	53 ± 6
10	H	Me	OCOMe	O	B	28	181–183	E	$C_{16}H_{18}N_2O_4$	H, N; C[h]	0.1	9 ± 6
											0.3	34 ± 2
											1.0	61 ± 7
11	H	CH_2Cl	OH	O	A	28	196–197	E	$C_{14}H_{15}N_2O_3Cl$	C, H, N	10.0	28 ± 1
12	H	CH_2OMe	OH	O	A	52	162–163	E	$C_{15}H_{18}N_2O_4$	C, H, N	0.3	16 ± 3
											1.0	32 ± 3
13	H	CH_2NHMe	OH	O	*a*	49	159–160.5	E	$C_{15}H_{19}N_3O_3$	H, N; C[i]	10.0	15 ± 9
14	H	Me	$\Delta^{3,4}$	O	*a*	10	146–147	Et	$C_{14}H_{14}N_2O_2$	C, H, N	1.0	20 ± 8
											3.0	52 ± 5
15	H	Me	H	O	*a*	15	166–167	E–P	$C_{14}H_{16}N_2O_2$	C; H, N[j]	0.3	18 ± 3
											1.0	44 ± 7
pinacidil											1.0	11 ± 2
											3.0	39 ± 7

[a] See the Experimental Section. [b] E = EtOAc, Et = Et_2O, H = hexane trituration, P = pentane. [c] Analyses for the elements indicated were within ±0.4% of the theoretical values. [d] Systolic blood pressure was measured at intervals from 1 to 6 h in groups of six SH rats per compound. [e] Reference 1. [f] N: calcd, 10.21; found, 9.65. [g] Calcd: N, 10.13; S, 11.60. Found: N, 9.38; S, 10.84. [h] C: calcd, 63.57; found, 62.93. [i] C: calcd, 62.67; found, 61.76. [j] Calcd: H, 6.60; N, 11.47. Found: H, 7.32; N, 10.92.

Table II. *trans*-6,7-Substituted-4-(acetylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols

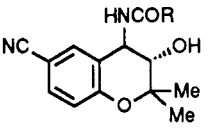


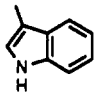
compd	R_1	R_2	% yield[a]	mp, °C	recryst[b] solvent	formula	anal.[c]	dose, mg/kg po	max fall[d] in BP, % ± SEM
16	H	H	44	206–207	E–P	$C_{13}H_{17}NO_3$	C, H, N	10.0	13 ± 2
17	Cl	H	22	186–188	E	$C_{13}H_{16}NO_3Cl$	C, H, N	1.0	8 ± 1
								10.0	34 ± 4
18	MeCO	H	10	182–183	E–P	$C_{15}H_{19}NO_4 \cdot 0.5H_2O$	C, H, N	0.1	20 ± 4
								0.3	23 ± 2
								1.0	61 ± 3
19	NO_2	MeCONH	23	256–259	E	$C_{15}H_{19}N_3O_6$	C, H, N	0.1	9 ± 6
								0.3	38 ± 6
20	MeCONH	NO_2	18	244–246	E	$C_{15}H_{19}N_3O_6$	C, H, N	3.0	16 ± 2
21	Br	NO_2	93	208–210	C	$C_{13}H_{15}N_2O_5Br$	C, H, N	0.3	25 ± 4
								1.0	51 ± 3
22	NC	NO_2	24[e]	215–217	E	$C_{14}H_{15}N_3O_5$	C, H, N	0.1	26 ± 6
								0.3	46 ± 5

[a] Method A. See the Experimental Section. [b] E = EtOAc, P = pentane, C = chromatography. [c,d] See footnotes *c* and *d* in Table I. [e] See the Experimental Section.

verted to the amides shown in Tables I–III by reaction with the appropriate acid chloride (method A), acetic anhydride (method B), acid (method C), or mixed anhydride (method D). Ureas **31–37** in Table IV were obtained by treating

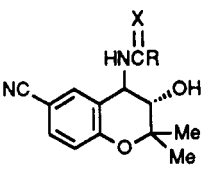
Table III. *trans*-4-(Substituted-aroylamino)-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols



compd	R	method[a]	% yield	mp, °C	recryst[b] solvent	formula	anal.[c]	dose, mg/kg po	max fall[d] in BP, % ± SEM
23	Ph	A	19	192.5–194	E–H	$C_{19}H_{18}N_2O_3$	H, N; C[e]	0.3	16 ± 3
								1.0	41 ± 8
24	Ph-3,4-C_4H_4	A	31	238–240	E–H	$C_{23}H_{20}N_2O_3$	C, H, N	1.0	6 ± 2
								10.0	35 ± 3
25		D	29	165	E–H	$C_{18}H_{17}N_3O_3$	C, H, N	0.1	22 ± 1
								0.3	36 ± 6
26		D	5	221–223	E	$C_{18}H_{17}N_3O_3$	C, H, N	0.3	27 ± 8
								1.0	43 ± 7
27		C	7	202–204	E	$C_{17}H_{17}N_3O_3$	C, H, N	0.3	12 ± 3
								1.0	50 ± 4
28		D	4	219–222	E	$C_{21}H_{19}N_3O_3 \cdot 0.25H_2O$	C, H, N	10.0	13 ± 1
29		A	55	207–209	E	$C_{17}H_{16}N_2O_4$	C, H, N	0.3	11 ± 4
								1.0	54 ± 6
30		D	4	238–239	C	$C_{17}H_{16}N_2O_4$	C, H, N	0.3	19 ± 4
								1.0	35 ± 9

[a] See the Experimental Section. [b] E = EtOAc, H = hexane, C = $CHCl_3$. [c,d] See notes *c* and *d* in Table I. [e] C: calcd, 70.79; found, 69.90.

Table IV. *trans*-4-(Substituted-amido)-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols



compd	X	R	% yield[a]	mp, °C	recryst[b] solvent	formula	anal.[c]	dose, mg/kg po	max fall[d] in BP, % ± SEM
31	O	NH_2	8	212–214	E	$C_{13}H_{15}N_3O_3$	C, H, N	1.0	18 ± 2
								3.0	46 ± 6
								10.0	56 ± 4
32	O	NHMe	51	143–146	M	$C_{14}H_{17}N_3O_3$	C, H, N	0.1	14 ± 4
								0.3	31 ± 9
								1.0	61 ± 3
33	S	NHMe	53	203–205		$C_{14}H_{17}N_3O_2S$	C, H, N	1.0	16 ± 2
								3.0	33 ± 3
								10.0	50 ± 1
34	O	$NH(CH_2)_3Me$	77	173–174		$C_{17}H_{23}N_3O_3$	C, H, N	1.0	11 ± 4
								10.0	29 ± 8
35	O	$NHC(Me)_3$	39	225–228	E	$C_{17}H_{23}N_3O_3$	C, H, N	10.0	8 ± 3
36	O	NHPh	85	226–227		$C_{19}H_{19}N_3O_3$	C, H, N	10.0	13 ± 3
37	O	$NHCOCCl_3$	41	231–233		$C_{15}H_{14}N_3O_4Cl$	C, H, N	1.0	13 ± 2
								10.0	28 ± 2
38	O	COOEt	50[e]	160–162	E	$C_{16}H_{18}N_2O_5$	C, H, N	10.0	12 ± 3
39	O	OEt	28[f]	147–148	E	$C_{15}H_{18}N_2O_4$	C, H, N	1.0	13 ± 6
								3.0	22 ± 5
								10.0	54 ± 3

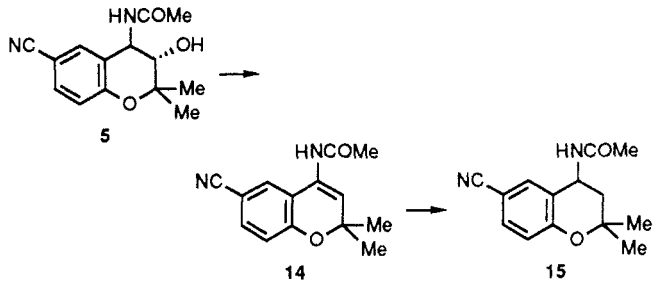
[a] Method E of the Experimental Section. [b] E = EtOAc, M = CH_2Cl_2. [c,d] See notes *c* and *d* in Table I. [e] Method A of the Experimental Section. [f] Method D of the Experimental Section.

4-amino compound **41** (R = CN, R_1 = H) with the appropriate isocyanate (method E). Compound **31** required in situ generation of the isocyanate.

Additional chemical manipulation of certain of the acyclic amides found in Tables I–III was required for the preparation of compounds **9**, **13**, **14** **15**, and **22**. Thus, compound **9** was obtained by treatment of compound **5** with Lawesson's reagent,[8] and compound **13** was obtained by treating (chloroacetyl)amino compound **11** with methylamine. Dehydration of dihydrobenzopyranol **5** (Scheme III) by boiling with 1 equiv of sodium hydride[1] in xylene furnished benzopyran **14**, which on catalytic hydrogenation yielded dihydrobenzopyran **15**. The 6,7-

(8) Pedersen, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293.

Scheme III



disubstituted analogue **22** (Table II) was prepared from compound **21** by treatment with copper(I) cyanide in *N*,*N*-dimethylformamide at 100 °C.

Results and Discussion

Compounds were evaluated for oral antihypertensive activity in the SHR. Systolic blood pressure, recorded from the tail, was determined before dosing and at various time intervals during the ensuing 6 h. Maximum falls in blood pressure obtained for all the compounds (Tables I–IV) occurred between 1 and 4 h postdose with some recovery to the predose level of blood pressure being observed at 6 h.

Initially the effect of variation in the alkyl groups flanking the 4-amido group of compound **2** was investigated by comparison with the close analogues **3**–**8** (see Table I). Extension of the alkyl group attached to the amide nitrogen atom, as in compound **4**, or reduction by one methylene unit, as in compound **3**, caused retention of the activity observed for compound **2**. However removal of the *N*-alkyl group caused a dramatic increase in activity, the acetylamino compound **5** being slightly more active than pyrrolidone **1**. While the secondary amidic nature of compound **5** was maintained, removal or extension of the alkyl group, as in compounds **6**–**8**, attenuated the activity associated with compound **5**.

Compounds **2**–**4** show in their NMR spectra two sets of signals for certain of the protons (see data for **3** in the Experimental Section). Variable temperature NMR spectroscopy shows that the signals coalesce at about 150 °C. The energy barrier to interconversion (approximately 18–20 kcal/mol) was estimated by using the equation[9] $\Delta G^{\ddagger} = [22.96 + \ln (T_c/\delta\upsilon)]RT_c$ (kcal/mol) and indicates that geometric isomerism about the tertiary amide bond is responsible for the effects observed in the NMR spectra of these compounds. Compound **5** shows no such isomerism, and the weaker activity of compounds **2**–**4** may, therefore, be partly ascribed to the presence of an isomer lacking the required geometry about the amide bond for antihypertensive activity.

Conversion of compound **5** to its thiocarbonyl analogue **9** or ester **10** gave compounds of similar activity. Incorporation of substituents in the acetylamino group, as in compounds **11**–**13**, caused activity to decline by various degrees compared with that of compound **5**.

The previous study[1] on the cyclic amido analogues recorded that, in those cases where comparisons could be made, the benzopyrans were as active as the 3,4-dihydrobenzopyran-3-ols. However in this series, compound **14**, although possessing good activity, was less active than the parent 3,4-dihydrobenzopyran-3-ol **5**. Restoration of sp^3 hybridization at C(3), as in dihydrobenzopyran **15**, partially restores the activity to the levels observed for compound **5**. This is in contrast to the earlier work[1] on the dihydrobenzopyran equivalent of compound **1**, wherein activity declined.

Table V. Increase in Rubidium Efflux in Rabbit Isolated Mesenteric Artery[a] for Certain Compounds Shown in Tables I–IV

compd	increase in ^{86}Rb efflux over basal rate, % ± SEM	compd	increase in ^{86}Rb efflux over basal rate, % ± SEM
1	110 ± 11 (n = 6)	**24**	17 ± 4 (n = 3)
pinacidil	72 ± 15 (n = 6)	**25**	53 ± 18 (n = 4)
5	59 ± 20 (n = 5)	**32**	63 ± 9 (n = 5)
18	38 ± 13 (n = 4)		

[a] See the Experimental Section.

Having established that in the 6-cyanobenzopyranols (Table I) the 4-acetylamino substituent confers the highest potency, inspection of the activities of the acetylamino analogues depicted in Table II confirms that, as in the previous series,[1] optimum activity is achieved when a strong electron-withdrawing group is located at C(6). Thus compounds **16** and **17** possess only weak activity, while acetyl analogue **18** has a similar activity to that of compound **5**. Of the 6,7-disubstituted compounds, compound **19** conforms to the requirement of a strong electron-withdrawing group at C(6), in contrast to compound **20** with the aromatic substituents reversed. The 6-bromo-7-nitro compound **21** shows good activity, and as a 6-bromo compound might, by analogy with the 6-chloro compound **17**, be expected to show only modest activity, this represents an additional example of the introduction of a 7-nitro group augmenting activity. This neighboring group effect has been observed in cyclic amino[7] and cyclic amido benzopyranols,[1] although its operation is not understood. Compound **22**, in which both the C(6) and C(7) substituents are strong electron-withdrawing groups, is the most active disubstituted compound in this series and thus extends the range of substituents which can be accepted in combination at C(6) and C(7) for good activity.

Since the size of the group (R_2) adjoining the amide carbonyl group was shown, in Table I, to be methyl for optimum activity, as in compound **5**, it was surprising to observe the activity of benzamide **23** (see Table III). Replacement of the benzamide group by the 2- or 3-pyridylamides (compounds **25** and **26**) retains the activity seen in benzamide **23**. Incorporation of pyrrole **27** and furan moieties **29** and **30** gave compounds of reasonable activity. In contrast, incorporation of bicyclic aromatic moieties as in naphthamide **24** and indole **28** only gave compounds of modest potency.

Other compounds containing the carbonylamino structural unit are presented in Table IV. Urea **31** was approximately 10-fold less active than the acetylamino compound **5**, but the additional methyl group (compound **32**) restored the activity to the level associated with compound **5**. The activity of methylurea **32** is attenuated by thiourea **33** formation, by increase in size of the alkyl group, as in compounds **34** and **35**, or by aromatic replacement, as in compound **36**. Of the remaining compounds in Table IV, only urethane **39** possessed reasonable activity, being about 10-fold less active than the methylurea **32**.

Mechanistic studies on lead compound **1** have been extended to include certain analogues described in this paper. Table V shows the increase in the basal efflux rate of rubidium-86,[10] a potassium ion surrogate, in the rabbit mesenteric artery preparation (see the Experimental Section) for these analogues in comparison with compound

(9) Abraham, R. J.; Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Heyden: London, 1980; p 167.

(10) Bolton, T. B.; Clapp, L. H. *J. Physiol. (London)* **1984**, *355*, 43.

1 and pinacidil. A concentration of 1×10^{-5} M was used for each of the compounds, as this concentration was found[3] to produce the maximum response for compound 1; higher concentrations produced a progressively smaller response. The efflux values obtained reflect only gross differences in the ability of the compounds to reduce blood pressure. For example, compound 1 is considerably more effective than compound 24 on both parameters, whereas compound 1 appears to be more effective than compound 5 on rubidium-86 efflux, although they are equally effective in lowering blood pressure. Perhaps it is not too surprising that an exact correlation is not obtained, since blood pressure lowering ability is determined in vivo in the SHR, whereas rubidium-86 efflux is determined in vitro in a different species.

Nevertheless, it can be seen that the antihypertensive mechanism of action of these 4-(substituted-carbonylamino)benzopyrans involves enhanced potassium ion efflux from vascular smooth muscle tissue and places them alongside their cyclic counterparts in the group of compounds termed the potassium-channel activators.

Experimental Section

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. NMR and mass spectra, which were in agreement with the structures cited, were recorded on a Varian EM 360A at 60 MHz, a Varian CFT-20 at 80 MHz, or a JEOL GX 270 for NMR and a VG 70-70, 70 ZAB, or JEOL DX 303 at 70 eV for MS. HF_{254} silica gel plates (2 mm) were used for chromatotron chromatography (radial chromatography).

6-Bromo-2,2-dimethyl-7-nitro-2*H*-1-benzopyran (43). A suspension of 6-amino-2,2-dimethyl-7-nitro-2*H*-1-benzopyran[5] (**42**, 5.0 g, 23 mmol) in glacial HOAc (19 mL) was added dropwise to a stirred solution of $NaNO_2$ (1.6 g, 23 mmol) in concentrated H_2SO_4 (19 mL) while the solution temperature was maintained below 10 °C. The solution was stirred for 0.5 h and added to a stirred solution of CuBr (6.5 g, 45 mmol) in 47% HBr (53 mL). The resulting solution was stirred for 1 h and then diluted with H_2O and extracted with EtOAc. The organic extract was washed with H_2O and $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The organic layer was filtered, evaporated, and chromatographed on silica gel. Elution with 3% EtOAc–petroleum ether (60–80 °C) gave the title compound **43** (3.5 g, 54%) as a gum: NMR ($CDCl_3$) δ 1.44 [s, 6 H, $C(Me)_2$], 5.75 (d, 9, H-3), 6.25 (d, 9, H-4), 7.16 (s, H-5, and H-8). Anal. ($C_{11}H_{10}NO_3Br$) C, H, N.

***trans*-3,6-Dibromo-3,4-dihydro-2,2-dimethyl-7-nitro-2*H*-1-benzopyran-4-ol (44).** To compound **43** (3.43 g, 12 mmol) in a stirred solution of Me_2SO (20 mL) and H_2O (2 mL) was added NBS (6.0 g, 34 mmol) in one portion. The solution was stirred at room temperature for 18 h, diluted with H_2O, and extracted with EtOAc to give a crude mixture which was boiled in dioxane (60 mL) and H_2O (30 mL) for 18 h. Dilution with H_2O and extraction with EtOAc gave compound **44** as a yellow solid (3.7 g, 81%). Recrystallization of a small portion from EtOAc–petroleum ether (60–80 °C) gave an analytical sample, mp 113–114 °C. Anal. ($C_{11}H_{11}NO_4Br_2$) C, H, N.

6-Bromo-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2*H*-1-benzopyran (40, R = 6-Br, 7-NO_2). Bromohydrin **44** (3.6 g, 9.5 mmol) and KOH pellets (4.0 g, 70 mmol) were stirred in dry Et_2O (0.5 L) at room temperature for 48 h. Filtration and evaporation gave epoxide **40** (R = 6-Br, 7-NO_2), as a pale yellow solid (2.47 g, 87%) which was used directly for conversion to the corresponding 4-amino-3-ol: NMR ($CDCl_3$) δ 1.05 [s, 3 H, $C(Me)_2$], 1.35 [s, 3 H, $C(Me)_2$], 3.25 (d, 4, H-3), 3.60 (d, 4, H-4), 7.00 (s, H-5), 7.40 (s, H-8).

***trans*-4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols (41).** Epoxides **40** (0.10 mol) and appropriate amines (1.0 mol) were stirred in EtOH (50–100 mL) for 2–4 days. Solvents were evaporated to give the crude amino alcohols **41** (90–95%) as solids which were used directly in methods A–E to prepare the majority of the compounds shown in Tables I–IV.

General Methods for the Preparation of Carbonylamino Compounds. Method A. *trans*-4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols (**41**, 0.01 mol) and triethylamine (0.01 mol) were stirred in CH_2Cl_2 (50 mL) and cooled to 0 °C. The appropriate acid chloride (0.01 mol) was added dropwise to the solution, and the mixture was stirred for 1 h at room temperature. Water was added cautiously, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. Filtration and evaporation gave the crude carbonylamino compounds, which were purified by recrystallization (see Tables I–IV). Compound **24**: NMR (CD_3OD) δ 1.36 [s, 3 H, $C(Me)_2$], 1.56 [s, 3 H, $C(Me)_2$], 3.88 (d, 10, H-3), 5.33 (d, 10, H-4), 6.93 (d, 9, H-8), 7.40–8.10 (series of m, 8 aromatic H), 8.50 (narrow m, H-5).

Method B. Compounds **41** (0.01 mol), NaOAc (0.05 mol), and Ac_2O (0.1 mol), were stirred at room temperature for 5–48 h with exclusion of moisture. Water was added cautiously to the solution, which was extracted with $CHCl_3$. The organic extract was washed with saturated $NaHCO_3$ solution, and dried over anhydrous $MgSO_4$. Filtration and evaporation gave the crude acetylamino compounds which were purified by recrystallization (see Table I). Compound **3**: NMR [$(CD_3)_2SO$] δ 1.18 and 1.22 [2 s, 3 H, $C(Me)_2$], 1.45 [s, 3 H, $C(Me)_2$], 2.17 and 2.22 (2 s, 3 H, COMe), 2.46 and 2.67 (2 s, 3 H, NMe), 3.67 (m, H-3, shape change on addition of D_2O), 3.63 and 4.78 (2 d, 10, H-4), 5.60 (overlapping signal at 4.78) and 5.95 (2 d, 6, OH exchangeable with D_2O), 6.93 and 6.97 (2 d, 9, H-8), 7.33 and 7.48 (2 narrow m, H-5), 7.59 and 7.63 (2 q, 9, 2, H-7).

Method C. To a stirred solution of the appropriate carboxylic acid (0.01 mol) in DMF (20 mL) cooled to 0 °C were added DCC (0.01 mol) and 1-hydroxybenzotriazole (0.009 mol), and the solution was stirred for 3 h. A solution of the appropriate amine **41** (0.01 mol) and triethylamine (0.01 mol) in DMF (20 mL) was added to the mixture which was stirred for 18 h and allowed to attain room temperature. The reaction mixture was filtered and evaporated and the residual gum was taken up in EtOAc, washed with brine and saturated Na_2CO_3 solution, and dried over anhydrous $MgSO_4$. Filtration, evaporation, and recrystallization furnished the carbonylamino compounds (see Tables I, III). Compound **6** was prepared by heating amine **41** (R = 6-CN, R_1 = H) with HCOOH. Workup was as described above.

Method D. To a stirred solution of the appropriate carboxylic acid (0.01 mol) and triethylamine (0.01 mol) in CH_2Cl_2 (120 mL) was added EtOCOCl (0.01 mol) in CH_2Cl_2 (60 mL) followed by a solution of the appropriate amine **41** (0.009 mol) in CH_2Cl_2 (60 mL) during 0.5 h, and the resulting mixture was stirred for 18 h at room temperature. The reaction mixture was washed with H_2O and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation gave the crude products which were usually chromatographed on silica gel using an EtOAc–pentane gradient elution, before recrystallization as described in Tables III–IV. Compound **30**: NMR ($CDCl_3$–CD_3OD) δ 1.36 [s, 3 H, $C(Me)_2$], 1.55 [s, 3 H, $C(Me)_2$], 3.78 (d, 10, H-3), 5.30 (d, 10, H-4), 6.91 (d, 10, H-8), 7.24 (m, 3 H, aromatic), 7.67 (narrow m, H-5), 7.93 (s, NH), 8.13 (m, 1 H, aromatic).

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(thioacetylamino)-2*H*-1-benzopyran-3-ol (9).** Compound **5** (0.52 g, 2 mmol) and Lawesson's reagent[8] (0.45 g, 1.14 mmol) were heated under reflux in dry PhMe (40 mL) for 1 h. The solution was cooled and evaporated to give a foam, which was chromatographed on silica gel (45 g) using $CHCl_3$ containing up to 10% EtOH in a gradient elution. Fractions containing the desired compound were combined (0.64 g) and radially chromatographed on silica gel and eluted with $CHCl_3$ to give a crude product (0.11 g) which was triturated with hexane to give compound **9** (80 mg, see Table I).

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-4-[[(methylamino)acetyl]amino]-2*H*-1-benzopyran-3-ol (13).** Compound **11** (0.25 g, 0.85 mmol) and 40% aqueous $MeNH_2$ (5 mL, 6.5 mmol) were stirred in EtOH (10 mL) at room temperature for 3 h. The solution was evaporated, taken up in EtOAc, washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting solid was recrystallized (see Table I) to give compound **13** (0.12 g).

Method E. Preparation of Ureas 32–37. The appropriate amine **41** (0.01 mol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred solution of the appropriate isocyanate (0.01 mol) in CH_2Cl_2 (15 mL), the temperature being maintained at below 10 °C. A white precipitate formed after 15 min and the reaction mixture was allowed to attain room temperature. The solid was

filtered and recrystallized to give the corresponding urea (see Table IV).

4-(Acetylamino)-6-cyano-2,2-dimethyl-2*H*-1-benzopyran (14). Compound **5**, (1.0 g, 4 mmol) and 80% NaH dispersion in oil (0.12 g, 4 mmol) were refluxed in dry $Ph(Me)_2$ (100 mL) under N_2 for 12–48 h. The reaction mixture was cooled, and H_2O (50 mL) was added cautiously to it. The layers were separated, and the organic layer was washed with H_2O and dried over anhydrous $MgSO_4$. Filtration, evaporation, radial chromatography using a pentane–EtOAc gradient elution, and recrystallization furnished the title benzopyran **14** (see Table I).

4-(Acetylamino)-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (15). Compound **14** (0.18 g, 0.74 mmol) and 10% Pd/C (0.1 g) were shaken in EtOH (25 mL) in an atmosphere of H_2 for 6 days. Filtration, evaporation, and radial chromatography using a 30% EtOAc–pentane gradient elution gave crystals (56 mg) which were purified (Table I) to give compound **15** (25 mg).

***trans*-4-[(Aminocarbonyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol (31).** To a stirred suspension of *trans*-4-amino-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol (**41**, R = 6-CN, R_1 = H; 1.0 g, 4.6 mmol) in H_2O (30 mL) at 0 °C was added 5 N HCl (0.92 mL). The stirred suspension was warmed to 70 °C, and MeOH (3 mL) and NaNCO (0.3 g, 4.6 mmol) were added to it. The solution was stirred for 2.5 h and cooled. The crystals which formed were filtered and recrystallized (see Table I) to give compound **31** (105 mg): NMR (CD_3OD) δ 1.29 [s, 3 H, $C(Me)_2$], 1.51 [s, 3 H, $C(Me)_2$], 3.55 (d, 9, H-3), 4.79 (d, 9, H-4), 6.88 (d, 9, H-8), 7.48 (q, 9, 2, H-7), 7.70 (narrow m, H-5).

***trans*-4-(Acetylamino)-6-cyano-3,4-dihydro-2,2-dimethyl-7-nitro-2*H*-1-benzopyran-3-ol (22).** 6-Bromo compound **21** (0.36 g, 1 mmol) was dissolved in DMF (5 mL) and CuCN (0.1 g, 1.1 mmol) was added to the solution, which was stirred at 100 °C for 6 h. The mixture was poured into H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and brine and dried over anhydrous $MgSO_4$. Filtration, evaporation, and purification (see Table II) gave compound **22** as a yellow solid (19 mg): NMR [$(CD_3)_2SO$] δ 1.23 [s, 3 H, $C(Me)_2$], 1.45 [s, 3 H, $C(Me)_2$], 3.62 (q, 9, 5, collapsing to d, 9, on addition of D_2O, H-3), 4.80 (t, 9, collapsing to d, 9, on addition of D_2O, H-4), 5.79 (d, 5, exchangeable with D_2O, OH), 7.73 (s, 1 H aromatic), 7.75 (narrow m, 1 H aromatic), 8.35 (d, 9, exchangeable with D_2O, NH).

Pharmacological Testing. Hypertensive Rats. All of the test compounds and the standard drug were evaluated for antihypertensive activity in conscious spontaneously hypertensive rats (14–24 weeks old), derived from the Japanese (Okamoto) strain. Animals with systolic blood pressure >180 mmHg (1 mmHg = 133 Pa) were considered to be hypertensive.

Systolic blood pressure was recorded by the tail-cuff method using a W+W BP recorder, Model No. 8005; each determination was the mean of at least six recordings. Blood pressure measurements were made prior to the oral administration of test compound and at intervals for up to 6 h postdose.

All compounds were administered (via an oral dosing needle placed in the esophagus) as a solution or suspension in 1% w/v methylcellulose solution.

With the use of the above procedure, vehicle alone typically has little or no effect on blood pressure apart from a slight reduction (by 5–10%) at 6 h postdose.

Isolated Rabbit Mesenteric Artery Preparation. The efflux of rubidium-86 from preloaded segments of New Zealand White rabbit isolated mesenteric arteries was determined essentially as described previously. Arteries were cut into segments of 10–20 mg wet weight and suspended for 30 min in a tissue bath containing about 200 mL of aerated (19:1 O_2–CO_2) HEPES buffer at 37 °C (mM composition: NaCl, 120.0; KCl, 6.0; $CaCl_2$, 2.5; $MgCl_2$, 1.2; HEPES, 5.0; glucose, 11.4; pH 7.4). 100–200 μCi of rubidium-86 (1–6 mCi per mg) was added to the bath, and the tissues were allowed to equilibrate for 90 min. Each tissue was subsequently transferred, at 3-min intervals, through a series of plastic vials containing 3 mL of radiolabel-free aerated buffer. The test compounds (1×10^{-5} M) were present in the vials from min 30 to 48 of the efflux period. The radioactive content of the vials was determined by liquid scintillation counting. The results are expressed as rate coefficients, which were calculated as the rubidium-86 released during each 3-min period as a percentage of the mean tissue rubidium-86 remaining during that period. The mean rate coefficient over min 21–30 of the efflux period was taken as the basal rate. Drug stimulation of efflux rate was calculated as the maximum efflux rate observed over min 30–45 of the efflux period, divided by the basal rate, and was expressed as a percentage, together with standard error (see Table V).

Acknowledgment. We wish to thank David Bragg, Catherine Fish, Frances Hicks, and Graham Moore for skilled technical assistance.

Registry No. (±)-**1**, 94470-67-4; (+–)-**2**, 128360-05-4; (+–)-**3**, 128360-06-5; (+–)-**4**, 128360-07-6; (+–)-**5**, 128360-08-7; (+–)-**6**, 128360-09-8; (+–)-**7**, 128360-10-1; (+–)-**8**, 128360-11-2; (+–)**9**, 128360-12-3; (+–)-**10**, 128360-13-4; (+–)-**11**, 128360-14-5; (+–)-**12**, 128360-15-6; (+–)-**13**, 12836-16-7; **14**, 89317-02-2; (±)-**15**, 128360-17-8; (+–)-**16**, 128388-11-4; (+–)-**17**, 128360-18-9; (+–)-**18**, 128360-19-0; (+–)-**19**, 128360-20-3; (+–)-**20**, 128360-21-4; (+–)-**21**, 128360-22-5; (+–)-**22**, 128360-23-6; (+–)-**23**, 128360-24-7; (+–)-**24**, 128360-25-8; (+–)-**25**, 128360-26-9; (+–)-**26**, 128360-27-0; (+–)-**27**, 128360-28-1; (+–)-**28**, 128360-29-2; (+–)-**29**, 128360-30-5; (+–)-**30**, 128360-31-6; (+–)-**31**, 128360-32-7; (+–)-**32**, 128360-33-8; (+–)-**33**, 128360-34-9; (+–)-**34**, 128360-35-0; (+–)-**35**, 128360-36-1; (+–)-**36**, 128360-37-2; (+–)-**37**, 128360-38-3; (+–)-**38**, 128360-39-4; (+–)-**39**, 128360-40-7; (+–)-**40** (R = 6-CN), 75611-72-2; (+–)-**40** (R = H), 87894-83-5; (+–)-**40**, 128360-44-1; (+–)-**40** (R = 6-MeCO), 123595-65-3; (+–)-**40** (R = 6-NO_2,7-MeCONH), 128360-45-2; (+–)-**40** (R = 6-MeCONH, 7-NOP_2), 103732-63-4; (+–)-**40** (R = 6-Br, 7-NO_2), 128360-46-3; (+–)-**40** (R = 6-CN, 7-NO_2), 128360-47-4; (+–)-**41** (R = 6-CN, R_1 = Et), 128360-41-8; (+–)-**41** (R = 6-CN, R_1 = Me), 128360-42-9; (+–)-**41** (R = 6-CN, R_1 = $(CH_2)_2$Me), 128360-43-0; (+–)-**41** (R = 6-CN, R_1 = H), 123595-70-0; (+–)-**41** (R = H, R_1 = H), 128360-48-5; (+–)-**41** (R = 6-Cl, R_1 = H), 128360-49-6; (+–)-**41** (R = 6-MeCO, R_1 = H), 128360-50-9; (+–)-**41** (R = 6-NO_2, 7-MeCoNH, R_1 = H), 103732-66-7; (+–)-**41** (R = 6-MeCoNH, 7-NO_2, R_1 = H), 103732-64-5; (+–)-**41** (R = 6-Br, 7-NO_2, R_1 = H), 128360-51-0; (+–)-**41** (R = 6-CN, 6-NO_2, R_1 = H), 128360-52-1; **42**, 64169-75-1; **43**, 108551-35-5; (+–)-**44**, 128360-53-2; 2-pyrrolecarboxylic acid, 634-97-9; 2-pyridinecarboxylic acid, 98-98-6; 3-pyridinecarboxylic acid, 59-67-6; 3-indolecarboxylic acid, 771-50-6; 3-furancarboxylic acid, 488-93-7; 2-naphthalenecarbonyl chloride, 2243-83-6; 2-furancarbonyl chloride, 527-69-5.