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Synthesis and Hypotensive Activity of Benzopyran Derivatives[1)]

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A series of dihydrobenzopyranyloxypropanolamines and dihydrobenzopyranylethanolamines containing a nitroxy moiety was synthesized. The cardiovascular effects of these compounds were investigated in anesthetized dogs. Some of the compounds exhibited hypotensive activity in combination with β-adrenergic blocking and vasodilating action. The structure–activity relationships are discussed.

Keywords——β-adrenergic blocking activity; vasodilating activity; antihypertensive drug; dihydrobenzopyran; nitrate; nipradilol

β-Adrenergic receptor antagonists (β-blockers) have been applied to the treatment of hypertension, but the onset of their actions is often slow and they are effective in only about 50% of hypertensive patients. Vasodilators that were similarly applied to the treatment of hypertension cause tachycardia, and so β-blockers are often prescribed in combination with vasodilators for the therapy of hypertension. In an attempt to obtain both β-blocking and vasodilative actions in a single molecule, we synthesized novel dihydrobenzopyran derivatives having the side chain characteristic of β-blockers and a nitroxyalkyl moiety that was expected to have vasodilating activity, and tested them for hypotensive activity in dogs.

Chemistry

The phenolic precursors (**25**—**28**) were prepared from methoxybenzopyrans[2)] (**21**—**24**) by catalytic hydrogenation and subsequent demethylation (Chart 1).

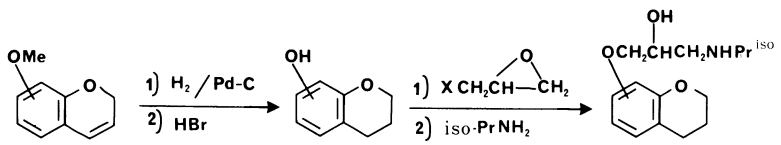
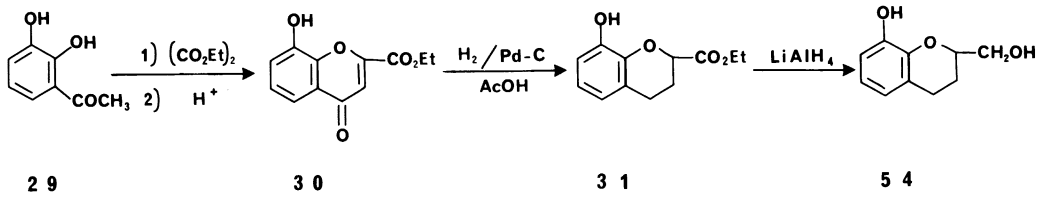


Chart 1

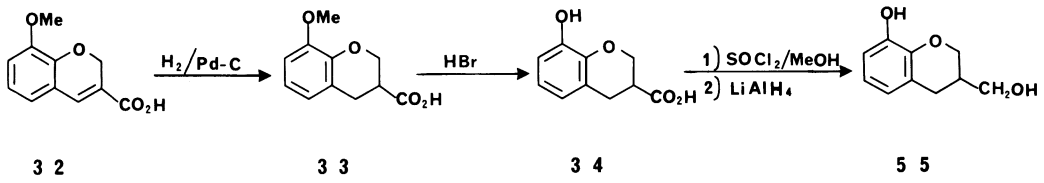
3,4-Dihydro-8-hydroxy-2-hydroxymethyl-2*H*-1-benzopyran (**54**) was prepared from 2′,3′-dihydroxyacetophenone (**29**) (Chart 2). Thus, condensation of **29** with diethyl oxalate and subsequent ring closure with conc. HCl gave chromone (**30**), which was hydrogenated on 10% Pd–C and subsequently reduced with $LiAlH_4$ to give **54**. 3,4-Dihydro-8-hydroxy-3-hydroxymethyl-2*H*-1-benzopyran (**55**) was prepared from 8-methoxy-2*H*-1-benzopyran-3-carboxylic acid[3)] (**32**) (Chart 3). Thus, catalytic hydrogenation of **32** on 10% Pd–C gave 3,4-

dihydro-8-methoxy-2*H*-1-benzopyran-3-carboxylic acid (**33**), which was demethylated with 47% HBr, followed by esterification and reduction with $LiAlH_4$ to give **55**. Similarly, ethyl 3,4-dihydro-8-methoxy-2*H*-1-benzopyran-4-carboxylate[4] (**35**) was led to 3,4-dihydro-8-hydroxy-4-hydroxymethyl-2*H*-1-benzopyran (**56**) (Chart 4).



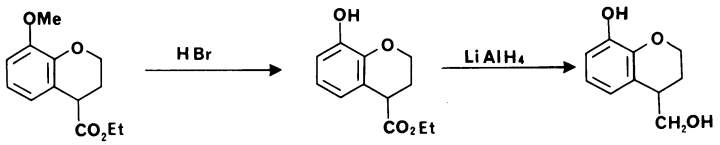
29 **30** **31** **54**

Chart 2



32 **33** **34** **55**

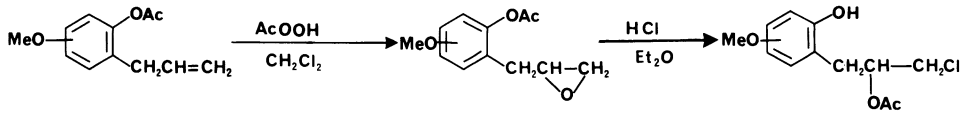
Chart 3



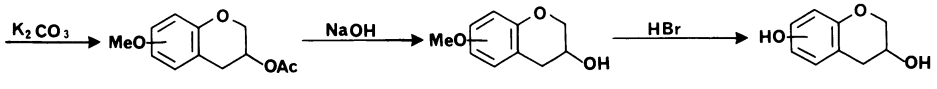
35 **36** **56**

Chart 4

Dihydroxybenzopyrans (**57**—**59**) were prepared from methoxy-2-allylphenylacetates[5] (**37**—**39**) (Chart 5). Thus, treatment[6] of **37**—**39** with 40% (w/v) peracetic acid in methylene chloride afforded epoxides (**40**—**42**), which were led to chlorohydrins (**43**—**45**), with opening of the epoxide ring and rearrangement of the acetyl moiety, by treatment with HCl. Ring closure of **43**—**45** with K_2CO_3 gave acetoxymethoxybenzopyrans (**46**—**48**), followed by hydrolysis and demethylation to give **57**—**59**.



37 — **39** **40** — **42** **43** — **45**



46 — **48** **49** — **51** **57** — **59**

Chart 5

6-Acetyl-3,4-dihydro-3,8-dihydroxy-2*H*-1-benzopyran (**60**) was obtained by acetylation of the diacetoxy compound (**52**) with acetyl chloride and $AlCl_3$ and subsequent hydrolysis with NaOH (Chart 6).

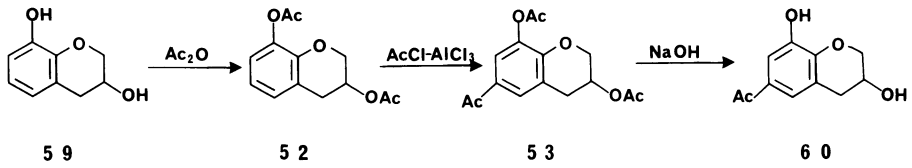


Chart 6

The nitrates (**61**—**67**) were prepared by acylation of hydroxyalkyl-3,4-dihydro-2*H*-1-benzopyrans (**54**—**60**) with acyl chloride and subsequent esterification with fuming nitric acid in acetic anhydride at low temperature and subsequent hydrolysis with NaOH. Glycidylation of compounds **25**—**28**, and **61**—**67** with epihalohydrin gave the epoxides, which were then aminated with the appropriate amines to produce the desired compounds (**1**—**17**) (Charts 1 and 7).

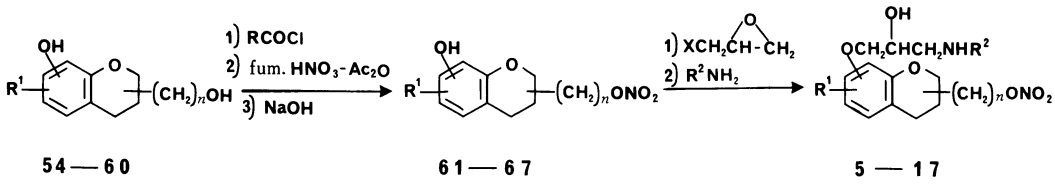
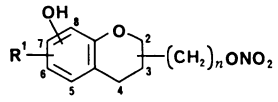


Chart 7

TABLE I. Hydroxynitroxyalkyl-3,4-dihydro-2*H*-1-benzopyrans

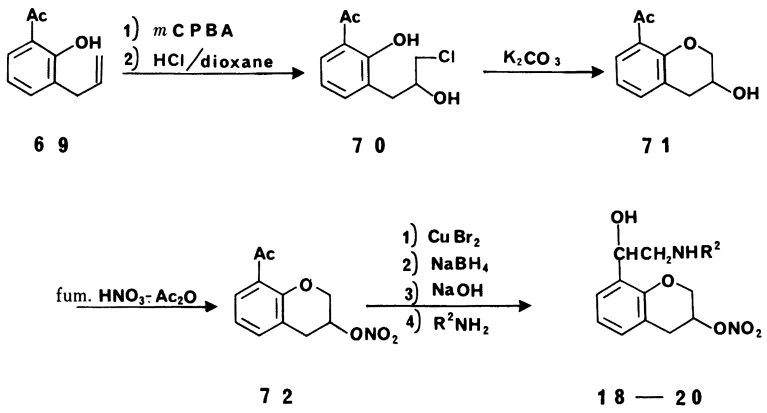


Compd. No.	OH	R^1	$(CH_2)_nONO_2$	Yield[a] (%)	mp (°C)	Formula[b]
61	8-OH	H	2-CH_2ONO_2	67	72—74	$C_{10}H_{11}NO_5$
62	8-OH	H	3-CH_2ONO_2	71	58—61	$C_{10}H_{11}NO_5$
63	8-OH	H	4-CH_2ONO_2	49	Oil	$C_{10}H_{11}NO_5$
64	5-OH	H	3-ONO_2	66	129	$C_9H_9NO_5$
65	6-OH	H	3-ONO_2	42	115—117	$C_9H_9NO_5$
66	8-OH	H	3-ONO_2	65	101—103	$C_9H_9NO_5$
67	8-OH	6-$COCH_3$	3-ONO_2	66	116—118	$C_{11}H_{11}NO_5$
68	8-OH	5,6-Br_2 (or 5,7-, or 6,7-)	3-ONO_2	73[c]	148—150	$C_9H_7Br_2NO_5$

a) Total yields of acylation, esterification and hydrolysis. *b*) All compounds were analyzed for C, H and N; the analytical results were within ±0.4% of the calculated values. *c*) Yield of bromination of **66** with *N*-bromosuccinimide.

The benzopyranylethanolamines (**18**—**20**) in Table IV were prepared by the route shown in Chart 8. Thus, epoxidation of 2-hydroxy-3-(2-propenyl)acetophenone[7] (**69**) with *m*-chloroperbenzoic acid, followed by treatment with HCl and cyclization with K_2CO_3 yielded 8-acetyl-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran (**71**). The nitrate (**72**) was obtained from **71**

by treatment with fuming nitric acid in acetic anhydride. Compounds **18**—**20** were synthesized from **72** according to the literature.[8]



6 9 7 0 7 1

7 2 1 8 — 2 0

*m*CPBA : *m*-chloroperbenzoic acid

Chart 8

Pharmacological Test Methods

Mongrel dogs (3 to 7 dogs per group), whose systolic blood pressure was 104 ± 3 mmHg and heart rate was 133 ± 3 bpm, were anesthetized with intravenous sodium pentobarbital. A cuffed endotracheal tube was inserted into the trachea, and respiration was maintained by means of a Harvard respirator. Catheters were placed in the aortic arch *via* the femoral artery for measurement of systemic blood pressure, and in the left femoral vein for drug administration. Systemic blood pressure was measured by a pressure transducer (Statham, P23ID). Heart rate was measured with a cardiotachometer triggered by the *R* wave of the electrocardiogram (the second limb lead). Pressure and heart rate were recorded on a linear recorder (Nihon Koden, WT 683G). A compound was administered by bolus intravenous injection in two or three dogs at a dose of 100 μg/kg, and the results are shown in Tables II—IV. Each compound was dissolved in saline or equimolar diluted hydrochloric acid, and the solution was diluted with saline to a final volume of 0.1 ml/kg.

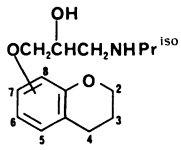
Results and Discussion

The effects of compounds **1**—**20** on blood pressure and heart rate are summarized in Tables II—IV. The introduction of an isopropylaminohydroxypropoxy side chain at the 5- or 8- position of the benzopyran ring resulted in a strong suppressive action on heart rate (compound **1** or **4**).

The nitrates are known to be typical vasodilators, and so we synthesized compounds **5**—**7**, introducing a nitroxyalkyl moiety into compound **4**. The hypotensive activity of these compounds was slightly stronger than that of compound **4**. However, the hypotensive activity was transient. It is likely that the nitrates of primary alcohols are easily reduced enzymatically. Therefore we synthesized the nitrates of secondary alcohols **8**—**10**. Compound **9** showed the strongest hypotensive activity among the tested compounds and the duration of action was long. However, it caused an increase in heart rate due to sympathetic reflex. Compound **10** showed strong hypotensive and negative chronotropic actions. In addition, the duration of action was very long (systemic blood pressure (SBP) reduction, 16 ± 3 mmHg; heart rate (HR) decrease, 16 ± 4 bpm).

Compounds **11**—**12**, derivatives of compound **10**, and compounds **13**—**17**, in which the

TABLE II. Dihydrobenzopyranyloxypropanolamines



Compd. No.	Position	Yield[a] (%)	mp (°C)	Formula[b]	SBP[c]		HR[d]	
					Change	Duration (min)	Change	Duration (min)
Propranolol[e]					−1	0	−3	30
Nitroglycerin[f]					−4	10	+3	3
1	5	13	65—68	$C_{15}H_{23}NO_3$	−1	30	−3	>30
2	6	59	78—81	$C_{15}H_{23}NO_3$	±	—	−1	30
3	7	48	97—99	$C_{15}H_{23}NO_3$	±	—	−1	30
4	8	15	78—79	$C_{15}H_{23}NO_3$	−1	30	−3	>30

a) Total yields of glycidylation and amination. *b*) See footnote *b* in Table I. *c*) Systemic blood pressure level is indicated as follows: (−1), 1—5 mmHg reduction; (−2), 6—10 mmHg reduction; (−3), 11—20 mmHg reduction; (−4), >20 mmHg reduction. *d*) Heart rates are indicated showed as follows: (+1), 1—5 beats per minute (bpm) increase; (+2), 6—10 bpm increase; (+3), 11—20 bpm increase; (−1), 1—5 bpm decrease; (−2), 6—10 bpm decrease; (−3), 11—20 bpm decreases; (−4), >20 bpm decrease. *e*) Dose: 100 μg/kg. *f*) Dose: 20 μg/kg.

isopropylamino moiety was replaced by other alkylamino groups, showed a weaker hypotensive activity than compound **10**. The order of potency of hypotensive action for amino substituents was iso-Pr > *tert*-Bu > Et > H.

Compounds **18**—**20**, aminoethanol derivatives, showed strong hypotensive and positive chronotropic actions.

These results suggest that the nitroglycerin-like action of a compound whose β-blocking action is weak may be strong. This study showed that compound **10** had the most desirable actions among the tested compounds. Therefore we selected compound **10** as a clinical candidate, and named it nipradilol. Furthermore, Uchida and coworkers[9] found that nipradilol had β-blocking and vasodilating actions in SHR not only on arterial but also on venous vessels, resulting in regulatory effects on pre- and after-load. Therefore, nipradilol may be a new type of antihypertensive drug.

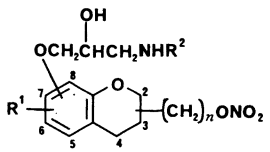
Experimental

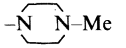
All melting points are uncorrected. Infrared (IR) spectra were measured with JASCO IRA-1 and Shimadzu IR-435 spectrometers. Proton magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a Varian EM-360 spectrometer and at 100 MHz with a JEOL JNM-MH-100 spectrometer. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, and br = broad. Mass spectra (MS) were measured with JEOL JMS-D-300 and JMS-D-100 mass spectrometers.

Hydroxy-3,4-dihydro-2*H*-1-benzopyrans (25—28) (Table V)——General Procedure: A solution of **21**—**24** (2.0 g) in AcOH (20 ml) was hydrogenated over 10% Pd–C (1.0 g) at room temperature under atmospheric pressure overnight. The catalyst was removed by filtration and washed with EtOH (20 ml). The filtrate and washings were combined and concentrated *in vacuo*. AcOH (5 ml) and 47% (w/v) HBr (20 ml) were added to the oily residue. The mixture was stirred at 100—110 °C for 1—2 h. The reaction mixture was concentrated to one-third of its original volume, then AcOEt (20 ml) and satd. brine were added. The AcOEt layer was washed with satd. brine and dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was then chromatographed on a silica gel column using benzene as an eluent to give pure **25**—**28**.

Ethyl 8-Hydroxy-4-oxo-4*H*-1-benzopyran-2-carboxylate (30)——A solution of 2′,3′-dihydroxyacetophenone

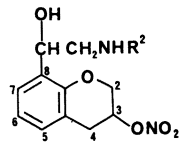
TABLE III. Nitroxyalkyldihydrobenzopyranyloxypropanolamines



Compd. No.	R^1	$-OCH_2CHCH_2NHR^2$ (OH)		$(CH_2)_nONO_2$	Yield[a] (%)	mp (°C)	Formula[b]	SBP[c]		HR[d]	
		Position	R^2					Change	Duration (min)	Change	Duration (min)
5	H	8	iso-Pr	2-CH_2ONO_2	49	85—86	$C_{16}H_{24}N_2O_6$	−1	5	−3	30
6	H	8	iso-Pr	3-CH_2ONO_2	64	59—61	$C_{16}H_{24}N_2O_6$	−2	5	−3	30
7	H	8	iso-Pr	4-CH_2ONO_2	39	122—123	$C_{16}H_{24}N_2O_6 \cdot H_2O$	−2	15	±	0
8	H	5	iso-Pr	3-ONO_2	52	82—85	$C_{15}H_{22}N_2O_6$	−1	5	−3	>30
9	H	6	iso-Pr	3-ONO_2	50	113—118	$C_{15}H_{22}N_2O_6$	−4	>30	+2	>30
10[e]	H	8	iso-Pr	3-ONO_2	61	110—122	$C_{15}H_{22}N_2O_6$	−3	>30	−3	>30
11	6-$COCH_3$	8	iso-Pr	3-ONO_2	61	107—110	$C_{17}H_{24}N_2O_7$	−1	5	±	0
12	5,6-Br_2 (or 6,7- or 7,8-)	8	iso-Pr	3-ONO_2	46	130—136	$C_{15}H_{20}Br_2N_2O_6$	−2	3	+3	3
13	H	8	*tert*-Bu	3-ONO_2	46	135—143	$C_{16}H_{24}N_2O_6(COOH)_2$	−2	20	−3	>30
14	H	8	Et	3-ONO_2	30	117—124	$C_{14}H_{20}N_2O_6$	−1	15	−4	>30
15	H	8	H	3-ONO_2	5	140—144	$C_{12}H_{16}N_2O_6 \cdot HCl \cdot H_2O$	−1	5	−3	>30
16	H	8	CH_2Ph	3-ONO_2	43	138—144	$C_{19}H_{22}N_2O_6$	−1	1	+1	3
17	H	8		3-ONO_2	58	115—125	$C_{17}H_{25}N_3O_6 \cdot 2HCl \cdot H_2O$	±	0	±	0

a) Total yields of glycidylation and amination. *b*) See footnote *b* in Table I. *c*, *d*) See footnotes *c*, *d* in Table II. *e*) Nipradilol.

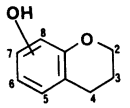
TABLE IV. Nitroxydihydrobenzopyranylethanolamines



Compd. No.	R^2	Yield[a] (%)	mp (°C)	Formula[b]	SBP[c] Change	SBP[c] Duration (min)	HR[d] Change	HR[d] Duration (min)
18	iso-Pr	31	125—134	$C_{14}H_{20}N_2O_5$	−4	>30	+3	>30
19	CH_2Ph	26	90—101	$C_{18}H_{20}N_2O_5$	−3	5	+3	3
20	$CH_2CH_2CH_2Ph$	15	93—101	$C_{20}H_{24}N_2O_5$	−3	5	+2	3

a) Total yields of bromination, reduction, hydrolysis and amination. *b*) See footnote *b* in Table I. *c*, *d*) Footnotes, *c*, *d* in Table II.

TABLE V. Hydroxy-3,4-dihydro-2*H*-1-benzopyrans



Compd. No.	R	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$)
25	5-OH	49	68—70	1.8—2.1 (2H, m), 2.5—2.8 (2H, m), 4.0—4.3 (2H, m), 5.7—6.1 (1H, br s), 6.2—6.5 (2H, m), 6.8—7.0 (1H, m)
26	6-OH	88	Oil	1.8—2.1 (2H, m), 2.5—2.8 (2H, m), 3.9—4.3 (2H, m), 6.4—6.8 (4H, m)
27	7-OH	23	Oil	1.8—2.1 (2H, m), 2.5—2.8 (2H, m), 4.0—4.2 (2H, m), 6.2—6.4 (2H, m), 6.8—6.9 (1H, m)
28	8-OH	60	Oil	1.8—2.1 (2H, m), 2.6—2.8 (2H, m), 4.1—4.3 (2H, m), 5.6 (1H, s), 6.4—6.8 (3H, m)

(**29**) (1.53 g) and diethyl oxalate (5.5 g) in EtOH (10 ml) was added to NaOEt (1.5 g) in EtOH (30 ml) at room temperature during 5 min, and the mixture was heated under reflux for 3 h. Conc. HCl (15 ml) was added to the reaction mixture, and the whole was heated under reflux for 3 h. A precipitate was removed by filtration, the filtrate was concentrated *in vacuo*, and AcOEt (150 ml) was added to the oily residue. The AcOEt extract was washed with H_2O, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was then purified on a silica gel column using $CHCl_3$–MeOH (10 : 1) as an eluent. Recrystallization from MeOH and AcOEt gave **30** (1.70 g, 72.6%) as colorless prisms, mp 196—200 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.47 (3H, t, J=6 Hz, CH_3), 4.45 (2H, q, J=6 Hz, CH_3), 6.98 (1H, s, C_3-H), 7.18—7.55 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1720 (COOEt), 1630 (CO). MS *m/z*: 234 (M^+).

3,4-Dihydro-8-hydroxy-2-hydroxymethyl-2*H*-1-benzopyran (54)——Compound **30** (11.4 g) was dissolved in AcOH (150 ml), and hydrogenated over 10% Pd–C (13.7 g) at 70 °C under atmospheric pressure for 4 h. The catalyst was filtered off, the filtrate was concentrated *in vacuo*, and anhydrous ether (140 ml) was added to the oily residue (**31**). The ether solution was added dropwise to $LiAlH_4$ (4.65 g) in anhydrous ether (70 ml) with stirring at 5 °C, and the whole was stirred at 10 °C for 2.5 h. The reaction mixture was added to an ice-cold mixture of H_2O (200 ml), AcOEt (200 ml) and 1 N HCl (50 ml). The organic layer was washed with H_2O, dried, and concentrated *in vacuo* to leave a brown solid. Recrystallization from AcOEt and hexane provided **54** (1.84 g, 21.0%) as colorless prisms, mp 146—148 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.50—2.05 (2H, m, C_3-H), 3.60—3.96 (2H, m, CH_2O), 4.00—4.30 (1H, m, C_2-H), 6.44—6.73 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 3340 (OH). MS *m/z*: 180 (M^+).

3,4-Dihydro-8-methoxy-2*H*-1-benzopyran-3-carboxylic Acid (33)——Compound **32** (21.0 g) in AcOH (300 ml) was hydrogenated over 10% Pd–C (10.0 g) at room temperature under atmospheric pressure for 12 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. Recrystallization of the crystalline residue from MeOH

provided **33** (7.5 g, 35.4%) as colorlss needles, mp 180—182 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 2.80—3.10 (3H, m, C_3-H and C_4-H), 3.80 (3H, s, OCH_3), 3.90—4.70 (2H, m, C_2-H), 6.60—6.80 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1698 (COOH). MS *m/z*: 208 (M^+).

3,4-Dihydro-8-hydroxy-2*H*-1-benzopyran-3-carboxylic Acid (34)——Compound **33** (10.4 g) was heated in 47% HBr (105 ml) at 120 °C for 1 h. The reaction mixture was cooled to 5 °C, and the resulting precipitate was filtered. Recrystallization from AcOEt provided **34** (6.75 g, 74.1%) as colorless prisms, mp 177—179 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 2.90—3.20 (3H, m, C_3-H and C_4-H), 3.98—4.70 (2H, m, C_2-H), 6.50—6.80 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1700 (COOH). MS *m/z*: 194 (M^+).

3,4-Dihydro-8-hydroxy-3-hydroxymethyl-2*H*-1-benzopyran (55)——Thionyl chloride (3.24 g) was added to **34** (3.53 g) in MeOH (35 ml) at 2 °C, and the reaction mixture was heated under reflux for 1 h, then evaporated *in vacuo*. The residue was dissolved in Et_2O (40 ml), and the solution was added to $LiAlH_4$ (2.08 g) in Et_2O (60 ml) at 1—3 °C. The mixture was stirred at 10 °C for 5 h and extracted with AcOEt (80 ml) after addition of aqueous HCl (50 ml). The AcOEt extract was washed with H_2O, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give **55** (2.92 g, 89.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.90 (3H, m, C_3-H and C_4-H), 3.40—3.70 (2H, m, CH_2OH), 3.80—4.35 (2H, m, C_2-H), 6.40—6.80 (3H, m, Ar-H). IR ν_{max}^{film} cm^{-1}: 3350 (OH). MS *m/z*: 180 (M^+).

3,4-Dihydro-8-hydroxy-4-hydroxymethyl-2*H*-1-benzopyran (56)——Compound **35** (4.10 g) was dissolved in AcOH (10 ml), the solution was added to 47% HBr (80 ml), and the mixture was stirred at 110 °C for 4 h, then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (100 ml). The $CHCl_3$ solution was washed with satd. brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give ethyl 3,4-dihydro-8-hydroxy-2*H*-1-benzopyran-4-carboxylate (**36**) (2.81 g) as a brown viscous oil. $LiAlH_4$ (2.21 g) was added to **36** (2.81 g) in anhydrous Et_2O (50 ml) at 1—3 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was added to ice-cold water (100 ml), and the whole was extracted with AcOEt (100 ml). The organic layer was washed with satd. brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to leave a brown viscous oil. The oil was chromatographed on a silica gel column using $CHCl_3$–MeOH (100 : 1, v/v) to give **56** (2.12 g, 67.9%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.96—2.20 (2H, m, C_3-H), 2.80—3.10 (1H, m, C_4-H), 3.70—3.96 (2H, m, CH_2O), 4.15—4.36 (2H, m, C_2-H), 6.60—6.85 (3H, m, Ar-H). IR ν_{max}^{film} cm^{-1}: 3350 (OH). MS *m/z*: 180 (M^+).

2-(2,3-Epoxy)propyl-6-methoxyphenyl Acetate (42)——A 40% (w/v) peracetic acid solution (3.0 ml) and AcOK (0.18 g) were added to 2-allyl-6-methoxyphenyl acetate (1.82 g) in CH_2Cl_2 (20 ml), and the mixture was stirred at room temperature for 48 h. The reaction mixture was added to $CHCl_3$ (100 ml) and 5% aqueous Na_2SO_3 (50 ml), and the $CHCl_3$–CH_2Cl_2 layer was washed with H_2O, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give **42** (1.74 g, 88.7%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, $-OCOCH_3$), 2.47—2.96 (4H, m, $-CH_2-\dot{C}H-\dot{C}H_2$), 3.00—3.35 (1H, m, $-CH_2-\dot{C}H-\dot{C}H_2$), 3.88 (3H, s, $-OCH_3$), 6.90—7.40 (3H, m, Ar-H).

2-(2-Acetoxy-3-chloro)propyl-6-methoxyphenol (45)——A 20% (w/v) ethereal HCl solution (5.0 ml) was added to **42** (1.74 g) in Et_2O (10 ml) at 0 °C, and the mixture was stirred at room temperature for 12 h. Et_2O (100 ml) was added to the reaction mixture, which was neutralized with saturated aqueous $NaHCO_3$. The Et_2O layer was washed with H_2O, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give **45** (1.83 g, 90.4%) as a pale yellow viscous oil. NMR ($CDCl_3$) δ: 2.09 (3H, s, $-OCOCH_3$), 2.90—3.34 (2H, m, $-CH_2-\dot{C}H-CH_2Cl$), 3.67—3.87 (2H, m, $-\dot{C}H-CH_2Cl$), 3.94 (3H, s, $-OCH_3$), 5.25—5.66 (1H, m, $-HC<$), 6.08 (1H, m, OH), 6.83—7.17 (3H, m, Ar-H).

3-Acetoxy-3,4-dihydro-8-methoxy-2*H*-1-benzopyran (48)——K_2CO_3 (1.26 g) was added to **45** (1.82 g) in *N*,*N*-dimethylformamide (DMF) (10 ml) with stirring at room temperature for 2 h. H_2O (50 ml) and benzene (100 ml) were then added to the reaction mixture, and the benzene layer was washed with H_2O, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give **48** (1.53 g) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, $-OCOCH_3$), 2.70—3.32 (2H, m, C_4-H), 3.88 (3H, s, $-OCH_3$), 4.08—4.48 (2H, m, C_2-H), 5.20—5.40 (1H, m, C_3-H), 6.60—6.98 (3H, m, Ar-H). IR ν_{max}^{film} cm^{-1}: 1731 ($OCOCH_3$). MS *m/z*: 222 (M^+).

3,4-Dihydro-3-hydroxy-8-methoxy-2*H*-1-benzopyran (51)——Compound **48** (1.53 g) was dissolved in MeOH (30 ml), and then 1 N NaOH (10 ml) was added to the MeOH solution. The mixture was stirred at room temperature for 1 h, added to 1 N HCl (12 ml), and concentrated *in vacuo*. The residue was extracted with benzene (30 ml). The benzene layer was washed with H_2O, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to leave a brown viscous oil. Crystallization of the oil from benzene–hexane provided **51** (0.66 g, 52.1%) as colorless prisms, mp 79—82 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.40—3.26 (3H, m, C_4-H and OH), 3.85 (1H, s, OCH_3), 3.87—4.20 (3H, m, C_2-H and C_3-H), 6.35—6.87 (3H, m, Ar-H). MS *m/z*: 180 (M^+).

3,4-Dihydro-3,8-dihydroxy-2*H*-1-benzopyran (59)——Compound **51** (1.50 g) was added to 47% HBr (8.60 g), and the mixture was stirred at 90 °C for 9 h. The reaction mixture was cooled to room temperature, made weakly acidic with aqueous NaOH, and extracted with AcOEt (30 ml). The AcOEt layer was washed with satd. brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to leave a brown solid, which was crystallized from acetone. Recrystallization from acetone and hexane gave **59** (1.23 g, 88.9%) as colorless needles, mp 126—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.56—3.20 (2H, m, C_4-H), 3.90—4.30 (4H, m, C_2-H, C_3-H and OH), 6.44—6.80 (3H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 3360 (OH). MS *m/z*: 166 (M^+).

3,4-Dihydro-3,5-dihydroxy-2*H*-1-benzopyran (57)——Compound **57** was synthesized from 2-allyl-3-methoxyphenyl acetate (**37**) *via* a route similar to that described above. Pale yellow viscous oil. ^{1}H-NMR (CD_3OD) δ:

2.40—3.10 (2H, m, C_4-H), 3.60—4.30 (3H, m, C_2-H and C_3-H), 6.24—6.44 (2H, m, Ar-H), 6.76—6.96 (1H, m, Ar-H). MS *m/z*: 166 (M^+).

3,4-Dihydro-3,6-dihydroxy-2*H*-1-benzopyran (58)——Compound **58** was synthesized from 2-allyl-4-methoxyphenyl acetate (**38**) *via* a route similar to that described above. Colorless needles (from acetone), mp 110—111 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 2.50—3.20 (2H, m, C_4-H), 3.70—4.50 (4H, m, C_2-H, C_3-H and OH), 6.45—6.80 (3H, m, Ar-H). MS *m/z*: 166 (M^+).

3,8-Diacetoxy-3,4-dihydro-2*H*-1-benzopyran (52)——Triethylamine (4.05 g) and Ac_2O (40.9 g) were successively added to a solution of **59** (16.7 g) in $CHCl_3$ (100 ml), and the mixture was stirred at room temperature for 12 h.Then 10% aqueous K_2CO_3 was added to the reaction mixture, and the $CHCl_3$ layer was washed with H_2O, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to leave pale yellow crystals. Recrystallization of the crystals from benzene and hexane gave **52** (21.0 g, 83.5%) as colorless prisms, mp 101—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, C_3-$OCOCH_3$), 2.28 (3H, s, C_8-$OCOCH_3$), 2.65—3.30 (2H, m, C_4-H), 4.10—4.35 (2H, m, C_2-H), 5.12—5.30 (1H, m, C_3-H), 6.80—7.00 (3H, m, Ar-H).

6-Acetyl-3,8-diacetoxy-3,4-dihydro-2*H*-1-benzopyran (53)——$AlCl_3$ (13.5 g) was added to **52** (12.6 g) in nitrobenzene (100 ml) at 1 °C during 0.5 h, and the mixture was stirred for 10 h at room temperature. Petroleum ether (800 ml) was added to the reaction mixture, the solvent was decanted off, and the residual brown viscous oil was partitioned between benzene (500 ml) and aqueous HCl (800 ml). The benzene layer was washed with H_2O, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The brown residue was chromatographed on a silica gel column using $CHCl_3$–benzene (1 : 1, v/v) as an eluent. Recrystallization of the crude crystals from benzene gave **53** (4.68 g, 31.8%) as colorless prisms, mp 155—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, C_3-$OCOCH_3$), 2.30 (3H, s, C_8-$OCOCH_3$), 2.50 (3H, s, C_6-$COCH_3$), 2.80—3.38 (2H, m, C_4-H), 4.10—4.46 (2H, m, C_2-H), 5.20—5.38 (1H, m, C_3-H), 7.49 (1H, d, J=2 Hz, Ar-H), 7.56 (1H, d, J=2 Hz, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1735 (CH_3COO), 1670. MS *m/z*: 292 (M^+).

6-Acetyl-3,4-dihydro-3,8-dihydroxy-2*H*-1-benzopyran (60)——A 2 N NaOH solution (15 ml) was added to **53** (3.03 g) in MeOH (25 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was adjusted to pH 4 with aqueous HCl, and extracted with AcOEt (350 ml). The AcOEt layer was washed with saturated brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. Recrystallization of the solid from AcOEt provided **60** as colorless needles, mp 185—187 °C. ^{1}H-NMR (CD_3OD–$CDCl_3$) δ: 2.50 (3H, s, $COCH_3$), 2.62—3.24 (2H, m, C_4-H), 7.20—7.30 (2H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 3390 (OH), 3160 (OH), 1655 ($COCH_3$). MS *m/z*: 208 (M^+).

Nitroxyalkyl-3,4-dihydro-2*H*-1-benzopyrans (61—67) (Table I)——General Procedure: A solution of 23 mmol of ethyl chloroformate (or trichloroacetyl chloride) in tetrahydrofuran (THF) (35 ml) was added to a solution of the appropriate hydroxyalkyl-3,4-dihydro-2*H*-1-benzopyran (**54—60**) (20 mmol) and triethylamine (23 mmol) in THF (20 ml) at 0—5 °C and the mixture was stirred at the same temperature for 0.5 h, then filtered. The filtrate was concentrated under reduced pressure. The residue (4.85 g) was dissolved in acetonitrile (80 ml), the solution was cooled to −8—−10 °C, and acetyl nitrate [prepared from Ac_2O (2.22 g) and fum. HNO_3 (1.36 g)] was added to the solution at −8 °C. The mixture was stirred at the same temperature for 0.5 h, and once again acetyl nitrate [prepared from Ac_2O (1.36 g) and fum. HNO_3 (0.85 g)] was added at −8 °C. The mixture was stirred at the same temperature for 0.5 h, quenched with aqueous $NaHCO_3$ and extracted with AcOEt (180 ml). The organic layer was washed with aqueous $NaHCO_3$ and satd. brine, dried, and evaporated to dryness. The residual brown oil was dissolved in a mixture of MeOH (10 ml) and a solution of NaOH (0.93 g) in H_2O (5 ml), and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was acidified with conc. HCl, freed of MeOH *in vacuo*, and extracted with AcOEt (60 ml). The extract was washed with satd. brine, dried, and evaporated to dryness. The residual dark brown oil was purified by silica gel column chromatography using benzene as an eluent. The solid eluate was crystallized from benzene and hexane to give the corresponding **61—67** as colorless crystals. The yields were generally 60—75%. 3,4-Dihydro-8-hydroxy-3-nitroxy-2*H*-1-benzopyran (**66**) afforded the following spectral data as an example of this class of compounds. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1620 and 1280 (ONO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.80—3.40 (2H, m, C_4-H), 4.08—4.49 (2H, m, C_2-H), 5.28—5.48 (1H, m, C_3-H), 5.49 (1H, s, OH), 6.48—6.89 (3H, m, Ar-H).

3,4-Dihydro-2*H*-1-benzopyranyloxypropanolamines (1—4) (Table II) and Nitroxyalkyl-3,4-dihydro-2*H*-1-benzopyranyloxypropanolamines (5—17) (Table III)——General Procedure: A solution of 4 mmol of the appropriate hydroxybenzopyran (**25—29**, **61—67**) in 1 N NaOH (15 ml) was treated with epichlorohydrin (16 mmol) and the whole was heated at 50 °C for 2 h. AcOEt (30 ml) was added to the reaction mixture and the organic layer was washed with 1 N NaOH (10 ml) and satd. brine (10 ml), dried, and evaporated to dryness. The residual oil was used without further purification. Thin layer chromatography (TLC) usually indicated a single product. 3,4-Dihydro-8-(2,3-epoxy)propoxy-3-nitroxy-2*H*-1-benzopyran afforded the following spectral data as an example of this class of compounds. ^{1}H-NMR ($CDCl_3$) δ: 2.64—3.26 (4H, m, C_4-H and –CH–CH_2O), 3.26—3.50 (1H, m, –CH–CH_2), 3.86—4.56 (4H, m, C_2-H and –OCH_2–), 5.32—5.52 (1H, m, C_3-H), 6.60—6.90 (3H, m, Ar-H). A solution of 4 mmol of the epoxide in MeOH (30 ml) was treated with alkylamine (20 mmol). The reaction mixture was heated at 70 °C for 1 h and evaporated to dryness. The residual brown oil was purified by Al_2O_3 column chromatography ($CHCl_3$). The solid eluate was crystallized from AcOEt and hexane. The total yield from the corresponding hydroxybenzopyran was generally 65—75%. The following spectral data were obtained for compound **10** (nipradilol) as an example of this class of compounds. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 3100 (OH), 1620 and 1280 (ONO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, d,

$J=6$ Hz, $-CH(CH_3)_2$), 2.40—3.42 (7H, m, C_4-H, $-CH_2NHCH$ and OH), 5.30—5.52 (1H, m, C_3-H), 6.54—6.86 (3H, m, Ar-H).

3-(3-Chloro-2-hydroxy)propyl-2-hydroxyacetophenone (70)——*m*CPBA (6.6 g) in CH_2Cl_2 (30 ml) was added to a solution of **69** (1.8 g) in CH_2Cl_2 (30 ml) at 3—8 °C, and the mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with $CHCl_3$ (30 ml), treated with 10% aqueous K_2CO_3 (30 ml) and 10% aqueous Na_2SO_3 (50 ml), washed with H_2O, and then dried over anhydrous sodium sulfate. Removal of the solvent from the filtrate under reduced pressure furnished the epoxide (1.83 g, 93.3%). A solution of the epoxide (1.83 g) in THF (10 ml) was treated with 18.5% HCl–dioxane (5 ml) at 5 °C for 1.5 h. The reaction mixture was poured into ice-cold H_2O (20 ml) and extracted with AcOEt (30 ml). Work-up of the AcOEt extract in the usual manner gave a product (2.36 g), which was purified by column chromatography (SiO_2 50 g, hexane : AcOEt = 15 : 1) to furnish **70** (1.21 g, 55.8%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s, CH_3), 2.96 (2H, d, $J=6$ Hz, CH_2), 3.50—3.65 (2H, m, CH_2Cl), 3.88—4.45 (1H, m, CH(OH)), 6.80—7.85 (3H, m, Ar-H). MS *m/z*: 228 (M^+).

8-Acetyl-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran (71)——K_2CO_3 (0.56 g) was added to a solution of **70** (0.46 g) in DMF (3 ml) at room temperature and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with H_2O (10 ml), and extracted with benzene (15 ml), and the extract was washed with H_2O (5 ml), then dried over sodium sulfate. Removal of the solvent from the filtrate under reduced pressure gave a product, which was purified by column chromatography (SiO_2 10 g, $CHCl_3$: MeOH = 100 : 1) to furnish **71** (0.25 g, 65.1%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s, CH_3), 2.85—3.10 (2H, m, C_4-H), 3.95—4.55 (3H, m, C_2-H and C_3-H), 6.90—7.85 (3H, m, Ar-H). MS *m/z*: 192 (M^+).

8-Acetyl-3,4-dihydro-3-nitroxy-2*H*-1-benzopyran (72)——Compound **71** (0.98 g) in acetonitrile (10 ml) was cooled to −35 °C and acetyl nitrate [prepared from Ac_2O (0.27 g) and fum. HNO_3 (0.13 ml)] was added to the solution at −30 °C. The mixture was stirred at the same temperature for 0.5 h, and once again the same quantity of acetylnitrate was added at −30 °C. The mixture was stirred at the same temperature for 0.5 h, quenched with aqueous K_2CO_3 and extracted with $CHCl_3$ (45 ml). The organic layer was washed with aqueous K_2CO_3 and satd. brine, dried and evaporated to dryness. The residual brown oil was purified by column chromatography (SiO_2 30 g, benzene : AcOEt = 50 : 1) to furnish **72** (0.95 g, 78.8%), which was crystallized from AcOEt–hexane to give colorless prisms, mp 80—83 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s, CH_3), 2.90—3.55 (2H, m, C_4-H), 4.30—4.80 (2H, m, C_2-H), 5.45—5.65 (1H, m, C_3-H), 6.92—7.80 (3H, m, Ar-H). MS *m/z*: 237 (M^+).

8-(2-Alkylamino-1-hydroxy)ethyl-3,4-dihydro-3-nitroxy-2*H*-1-benzopyran (18—20) (Table IV)——Compounds **18**—**20** were prepared by the literature procedure. IR ν_{max}^{KBr} cm^{-1}: 1620—1622 and 1275—1278 (ONO_2). ^{1}H-NMR ($CDCl_3$) δ: 4.10—4.40 (2H, m, C_2-H), 4.90—5.20 (1H, m, CH(OH)), 5.30—5.60 (1H, m, C_3-H).

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References and Notes

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