h. EtOH (20 mL) was added and the solution was heated at 55–60 °C for 16 h. Dry air was then bubbled into the solution for 4 h while the volume of EtOH was maintained at approximately 15–20 mL. The volume was then reduced to 5–10 mL and chilled to give 398.4 mg (56.1%) of a violet-blue solid. Recrystallization from benzene gave 362 mg (51.0% yield) of amino derivative **7**, mp 172–173 °C. Anal. ($C_{27}H_{36}N_4O_5$) C, H, N.

Preparation of the Hydrochloride Salt. To the free amine (271.5 mg) in 100 mL of isopropyl alcohol was added 3 mL of concentrated HCl and the solution was evaporated on a rotary evaporator at 40 °C. Benzene (50 mL) and EtOH (50 mL) were added, and the solution was again evaporated. Then 50 mL of isopropyl alcohol was added and the solution was evaporated. The compound was recrystallized from isopropyl alcohol to give 161.3 mg of the deep blue dihydrochloride, mp 239–240 °C. Anal. ($C_{27}H_{38}Cl_2N_4O_5 \cdot 0.5H_2O$) C, H, N, Cl.

Growth Inhibition Studies. IC_{50} Determinations. Leukemia L1210 cells were diluted to a concentration of 1×10^5 cells/mL in RPMI 1640 plus 20% HI-FCS plus 20 mmol Hepes. Cells were distributed into 13 × 100 mm sterile, borosilicate-glass culture tubes and randomized before 1-mL aliquots of test compound or control solution were added. This 1:2 dilution of cells with test solution resulted in a final inoculum of 5×10^4 cells/mL in a 2-mL total volume of RPMI 1640 plus 10% HI-FCS 20 mmol Hepes. Tubes were stoppered with silicon stoppers and incubated in an upright position in a 37 °C incubator for 48 h.

Following incubation, growth (cells/mL) was determined with a Coulter electronic cell counter. Calculations and graphing of data were performed with an Apple computer. For each concentration of compound, the program averaged the triplicates and calculated the percent control growth. The percent control growth was plotted versus compound concentration and the IC_{50} value was determined.[25]

Human nonsmall cell lung carcinoma H125, human breast carcinoma MCF7, human ovarian carcinoma A121, and human colon carcinoma WiDr cells (NCI Tumor Repository, Frederick MD) were harvested from stock cultures and added (1000–3000 cells/well) to 96-well tissue culture trays. Drug was added to each column (eight replicates) of wells in a stepwise fashion to achieve final drug concentrations ranging from 10^{-4} to 10^{-8} M. Cell growth inhibition was determined 3–5 days later with a microculture tetrazolium assay (MTT), which was based on the enzymatic reduction of colorless MTT to a purple formazan product soluble in DMSO. Absorbance at 570 nm was proportional to cell number.[26] Color formation was measured with a Biotech plate reader and data analysis was performed by an IBM software system. The drug concentration which inhibits 50% of tumor growth (IC_{50}) was determined.

Therapeutic Efficacy of 7 in Mice with L1210 Leukemia. Groups of 5 DBA/2J mice were inoculated ip with 10^6 L1210 leukemia cells and demonstrated a statistically significant ($p < 0.01$), 38% increase in life span following the daily ip administration of 5 mg/kg of **7** (day 1–5). A group of 20 control mice showed survival times ranging between 6 and 8 days with a median of 7 days and a mean of 6.6 ± 0.13. Dosages above 20 mg/kg × 5 were toxic, resulting in loss of animal weight and early death.

These results are comparable to reported work where $CD2F_1$ mice inoculated with 10^5 L1210 leukemia cells and treated with 3.1 mg/kg DHAQ on days 1, 5, and 9 showed a 43% ILS.[18]

Acknowledgment. This project was supported by the American Cancer Society with Grant No. CH391.

(25) Bobek, M.; An, S.-H.; Skrincosky, D.; De Clercq, E.; Bernacki, R. J. *J. Med. Chem.* **1989**, *32*, 799.
(26) Alley, M. C.; et al. *Cancer Res.* **1988**, *40*, 569.

Synthesis and Antihypertensive Activity of 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyrans and Related Compounds, New Potassium Channel Activators

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The synthesis and antihypertensive activity of 4-(1,2-dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyran-3-ols are described. The unsubstituted pyridone adduct lead compound **7e** is highly active, with substituents on the pyridone ring leading to a decrease in activity. Strongly electron-withdrawing substituents at the C-6 position are required for optimal activity. When the 2-pyridone ring is replaced by other heterocycles such as 4-pyridone, pyrimidone, pyridazinone, pyrazinone, and 1,4-butanesultam, the activity is maintained. The removal of the 3-hydroxy function (→ **17a**) does not significantly reduce the activity. The elimination of water from the chromanols leads to the formation of the chromenes, which are among the most potent antihypertensives known. The influence of diverse substituents, in particular heterocyclic C-6 substituents, was investigated in the 4-(2-oxo-1-pyrrolidinyl)chroman-3-ol series. Chromanols esterified at the 3-hydroxy group with short-chain acids, maintain their activity. The epoxidation of the chromene double bond also produces active compounds. The rearrangement of the epoxides **22** produces the 3-keto compounds **23** and the enol derivatives **25**. The reduction of the ketone **23a** produces *cis*-chromanol **7ab** along with its trans isomer **7e**. All compounds were tested for oral antihypertensive activity in spontaneously hypertensive rats with a dose of 1 mg/kg; for selected compounds ED_{30} values as well as the duration of the antihypertensive effect were determined. 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (**18a**) is under development as a coronary vasodilator and a drug for treating angina pectoris.

Sodium channel blockers have been used for many years as local anesthetics and antiarrhythmics. Subsequently calcium channel blockers underwent a vigorous development resulting in a number of drugs that are now widely used in a range of indications. Currently there is a growing interest in the therapeutic potential of substances that modulate potassium channels.[1] There are three prototypes of this class of compounds: Pinacidil, a peripheral vasodilator; Nicorandil, an antianginal agent, and Cromakalim (**20a**), a highly potent antihypertensive drug.

Evans et al.[2] were able to show that the existence of a powerful electron-withdrawing group located at C-6 in benzopyran compounds as well as a 4-(cyclic amido) group is essential for good blood-pressure-lowering action in the

(1) Cook, N. S. *Trends Pharmacol. Sci.* **1988**, *9*, 21.
(2) 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.

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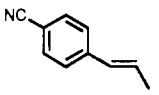
Table I. Substituted *trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2*H*-1-benzopyrans **7**

no.	R_1	R_2	R_3	R_4	R_5	yield, %	mp, °C	recryst solvent[a]	formula	anal.[b]	max fall[c] in BP in mmHg ± SEM in SHR
7a	$-(CH_2)_4-$	CN	H	H	H	43	225–227	A	$C_{19}H_{18}N_2O_3$	C,H,N	NS[d]
7b	$-(CH_2)_4-$	NO_2	H	H	H	14	249	B	$C_{18}H_{18}N_2O_5$	C,H,N	NS
7c	$-(CH_2)_5-$	CN	H	H	H	48	240–242	A	$C_{20}H_{20}N_2O_3$	C,H,N	NS
7d	$-(CH_2)_5-$	NO_2	H	H	H	29	247	C	$C_{19}H_{20}N_2O_5$	C,H,N	NS
7e	Me	CN	H	H	H	61	245–246	D	$C_{17}H_{16}N_2O_3$	C,H,N	108 ± 1
7f	Me	COMe	H	H	H	43	253–255	A	$C_{18}H_{19}NO_4$	C,H,N	38 ± 10
7g	Me	CN	Br	H	Br	9	207–209	B	$C_{17}H_{14}Br_2N_2O_3$	C,H,Br,N	NS
7h	Me	NO_2	H	H	H	29	229–231	E	$C_{16}H_{16}N_2O_5$	C,H,N	113 ± 7
7i	Me	CN	H	H	NO_2	14	249–251	B	$C_{17}H_{15}N_3O_5 \cdot 0.2H_2O$	C,H,N	23 ± 7
7j	Me	CN	NO_2	H	H	29	236–238	B	$C_{17}H_{15}N_3O_5$	C,H,N	NS
7k	Me	COOEt	H	H	H	54	213	B	$C_{19}H_{21}NO_5$	C,H,N	NS
7l	Me	CN	Cl	H	Cl	28	182–185	H	$C_{17}H_{14}Cl_2N_2O_3$	*e*	NS
7m	Me	CN	H	H	Cl	6	268–270	B	$C_{17}H_{15}ClN_2O_3$	C,H,N,Cl	37 ± 13
7n	Me	CN	H	H	NH_2	4	259–261	B	$C_{17}H_{17}N_3O_3$	C,H,N	34 ± 5
7o	Me	COOMe	H	H	H	55	267–268	A	$C_{18}H_{19}NO_5$	C,H,N	49 ± 4
7p	Me	CN	NH_2	H	H	48	216–218	C	$C_{17}H_{17}N_3O_3 \cdot 0.6H_2O$	C,H,N	NS
7q	Me	4-pyridyl	H	H	H	48	216–218	D	$C_{21}H_{20}N_2O_3$	C,H,N	24 ± 8
7r	Me	CN	H	H	COOH	34	259–261	C	$C_{18}H_{16}N_2O_5$	C,H,N	NS
7s	Me	CN	COOH	H	H	15	250–253	E	$C_{18}H_{16}N_2O_5 \cdot 0.25H_2O$	C,H,N	24 ± 8
7t	Me	CN	H	H	NHCOMe	23	303–305	C	$C_{19}H_{19}N_3O_4$	C,H,N	NS
7u	Me	CN	NHCOMe	H	H	43	274–276	B	$C_{19}H_{19}N_3O_4$	C,H,N	22 ± 11
7v	Me	CN	OCOMe	H	H	13	261–264	B	$C_{19}H_{18}N_2O_5$	H;C,N[f]	NS
7w	Me	CN	OMe	H	H	46	246–248	B	$C_{18}H_{18}N_2O_4 \cdot 0.3H_2O$	C,H,N	NS
7x	Me	$CSNH_2$	H	H	H	63	226–228	C	$C_{17}H_{18}N_2O_3S \cdot 0.5H_2O$	C,H,N,S	NS
7y	Me	CN	H	OBzl	H	15	238–240	A	$C_{24}H_{22}N_2O_4$	C,H,N	NS
7z	Me	CN	H	OMe	H	23	228–230	E	$C_{18}H_{18}N_2O_4$	C,H,N	73 ± 6
7aa	Me	CN	H	OEt	H	19	210–212	E	$C_{19}H_{20}N_2O_4$	C,H,N	NS
7ab[g]	Me	CN	H	H	H	4	210–212	E	$C_{17}H_{16}N_2O_3 \cdot 0.1H_2O$	C,H,N	26 ± 5
7ac	Me	CHO	H	H	H	20	222–224	B	$C_{17}H_{17}NO_4 \cdot 0.2H_2O$	C,H,N	NS
7ad	Me	CN	$N(CH_3)_2$	H	H	8	177–179	B	$C_{19}H_{21}N_3O_3$	C,H,N	NS
7ae	Me		H	H	H	19	245–247	A	$C_{25}H_{22}N_2O_3$	C,H,N	NS
7af	Me		H	H	H	12	190–192	E	$C_{19}H_{18}N_2O_3$	C,H,N	25 ± 5
7ag	Me	Br	H	H	H	47	228	D	$C_{16}H_{16}BrNO_3$	C,H,Br,N	NS

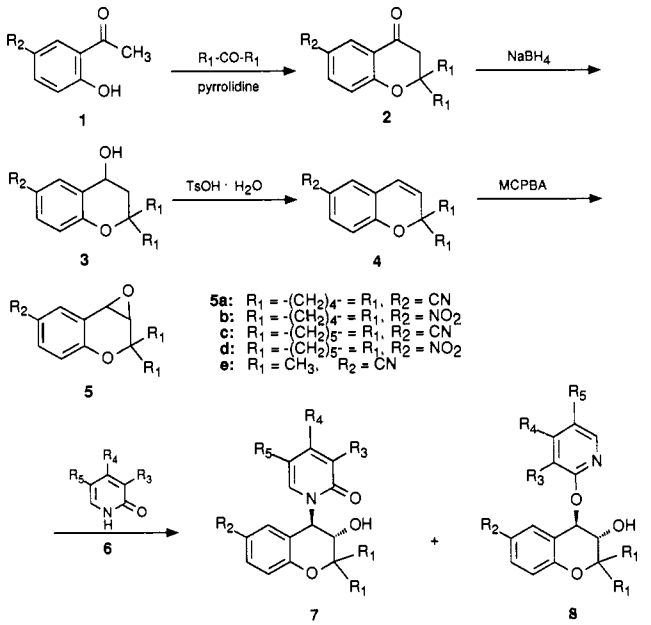
[a] A = EtOH; B = EtOAc; C = MeOH; D = Me_2CHOH; E = Et_2O; F = MeCN; G = $(Me_2CH)_2O$; H = CH_2Cl_2. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] Mean arterial blood pressure ($N \geq 3$) was measured directly before and up to 210 min after oral administration of 1 mg/kg of the test substance. [d] Compounds that did not lower the blood pressure significantly (<18 mmHg). [e] Consistent analyses could not be obtained. $C_{17}H_{14}Cl_2N_2O_3$ found m/z 364.0275, calcd 364.0276 (MS). [f] C: calcd, 64.40; found, 65.01; N: calcd, 7.91; found, 8.70. [g] Cis 3,4 isomer.

spontaneously hypertensive rat (SHR). While Evans et al. only described saturated 4-(cyclic amido) groups such as 2-pyrrolidinone and 2-piperidinone, we were surprised to find that these groups can be replaced by unsaturated 6-membered-ring heterocycles such as 2-pyridone, 4-pyridone, 6-pyridazinone, pyrimidone, and pyrazinone. All these heterocycles can be substituted by different ligands.

Chemistry

The (±)-epoxides **5**[2,3] served as starting materials for the synthesis of new 4-heterocyclic substituted 2*H*-1-benzopyran-3-ols shown in Tables I and II. 3,4-Epoxy-3,4-dihydro-2,2-dimethyl-6-(4-pyridyl)-2*H*-1-benzopyran was prepared from 4-(4-pyridyl)phenol[4] in the usual way. In the case of spiro compounds **5a–d** the 2-spirocyclical substituted 4-chromanones **2** were prepared either from 3-acetyl-4-hydroxybenzonitrile[5] or from 6′-hydroxy-3′-nitroacetophenone[6] by Kabbe's[7] method (Scheme I; only relative stereochemistry is shown). Borohydride reduction (→ **3**) and dehydration[8] with an acidic catalyst produced

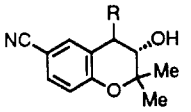
Scheme I

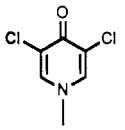
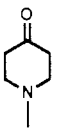
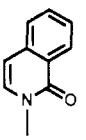
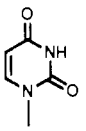
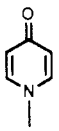
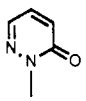
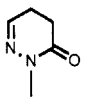
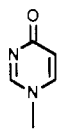
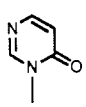
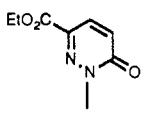
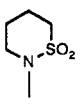
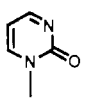
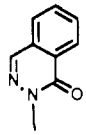


the 2-spiro-benzopyran compounds **4**, which were epoxidized[9] with *m*-chloroperbenzoic acid to **5**. This sequence

(3) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1983**, *26*, 1582.
(4) Lesher, G. Y.; Singh, B. U.S. Pat. 4297363, 1981.
(5) Ellis, G. P.; Show, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 779.
(6) Joshi, S. S.; Singh, H. *J. Am. Chem. Soc.* **1954**, *76*, 4993.
(7) Kabbe, H. J. *Synthesis* **1978**, 886.
(8) Lockhard, I. M. *Chromenes, Chromanones and Chromones*, G. P. Ellis, Ed.; John Wiley & Sons; New York, 1977; pp 150, 182.
(9) Lang, R. W.; Wenk, P. F. *Helv. Chim. Acta* **1988**, *71*, 596.

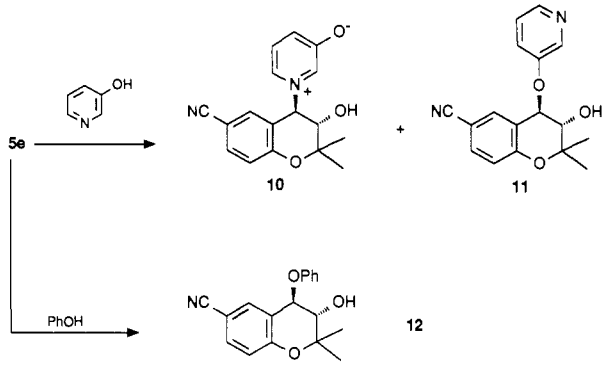
Table II. 4-Substituted *trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitriles **9**



no.	R	yield, %	mp, °C	recryst solvent	formula	anal.[b]	max fall[c] in BP in mmHg ± SEM in SHR
9a		34	>250	EtOAc	$C_{17}H_{14}Cl_2N_2O_3$	C,H,Cl,N	NS[d]
9b		11	142–145	Et_2O	$C_{17}H_{20}N_2O_3$	C,H,N	NS
9c		29	133–135	Et_2O	$C_{21}H_{18}N_2O_3$	C,H,N	24 ± 4
9d		43	>300	MeOH	$C_{16}H_{15}N_3O_4 \cdot 0.25H_2O$	C,H,N	NS
9e		85	299–301	EtOAc	$C_{17}H_{16}N_2O_3$	C,H,N	21 ± 3
9f		32	216–218	Et_2O	$C_{16}H_{15}N_3O_3 \cdot 0.25H_2O$	C,H,N	77 ± 5
9g		7	163–165	Et_2O	$C_{16}H_{17}N_3O_3$	C,H,N	63 ± 9
9h		16	307–310	MeOH	$C_{16}H_{15}N_3O_3$	C,H,N	18 ± 8
9i		21	207–208	MeOH	$C_{16}H_{15}N_3O_3$	C,H,N	19 ± 11
9j		65	259–261	EtOH	$C_{19}H_{19}N_3O_5$	C,H,N	24 ± 7
9k		57	212	Me_2CHOH	$C_{16}H_{20}N_2O_4S$	C,H,N,S	30 ± 9
9l		34	255–257	EtOH	$C_{16}H_{15}N_3O_3$	C,H,N	75 ± 17
9m		54	250–252	$(Me_2CH)_2O$	$C_{16}H_{15}N_3O_3$	C,H,N	20 ± 7
9n		14	192–194	EtOAc	$C_{20}H_{17}N_3O_3 \cdot 0.25H_2O$	C,H,N	38 ± 3

[b–d] See footnotes in Table I.

Scheme II



is also suitable for the preparation of analogous compounds such as **5e**.

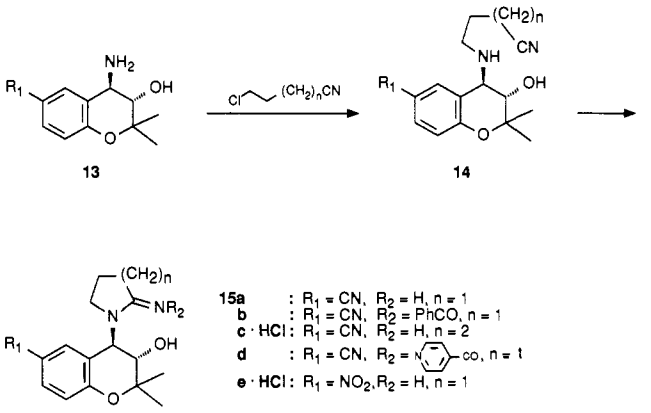
When the epoxides **5** are reacted with 2-pyridones **6** with pyridine in alcohol, the main products are the (±)-*trans*-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyran-3-ols **7**, frequently obtained directly in pure crystalline form (Table I). The byproducts, the (±)-*trans*-3,4-dihydro-4-(2-pyridyloxy)-2*H*-1-benzopyran-3-ols **8**, were only isolated in a few cases. When necessary, **7** and **8** can easily be separated by chromatography on silica gel because of the great difference in polarity.

The amines **7n** and **7p** were prepared by catalytic hydrogenation of the nitro compounds **7i** and **7j**, respectively. The thioamide **7x** was prepared by H_2S addition to the nitrile **7e** and the aldehyde **7ac** was also produced from **7e** by transfer hydrogenation using Raney nickel/hypophosphite.[10] The Wittig–Horner products **7ae** and **7af** were obtained from the aldehyde **7ac** with the (4-cyanobenzyl)phosphonate and the (cyanomethyl)phosphonate. The examples **9a–n** in Table II show that not only 2-pyridones but also 4-pyridones, pyridazinones, pyrimidones, pyrazinones, 1,4-butanesultames, and others can be reacted with the epoxide **5e**, also under standard conditions with pyridine/ethanol. For the reaction of **5e** with 4-piperidone hydrate hydrochloride (→ **9b**) and pyrimidin-2-ol hydrochloride (→ **9m**), triethylamine and an excess of sodium ethoxide, respectively, were used as the base instead of pyridine. The reaction of **5e** with 1,4,5,6-tetrahydropyridazin-6-one[11] (→ **9g**) was carried out according to the method of Evans et al.[2] (DMSO/NaH).

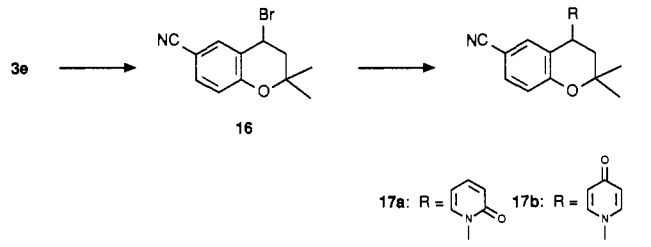
When **5e** is treated with pyrimidin-4-ol, the two possible isomers **9h** and **9i** are formed in almost equal quantities. The structures were determined by the calculation of increments in the chemical shifts of the pyrimidone protons and comparison with the measured NMR values. Differentiation is also possible, as all the 2-pyridone compounds **7** and their analogues, in contrast to the corresponding 4-pyridone compounds, produce a double set of signals in the NMR spectrum at room temperature in DMSO, which indicates a mixture of conformers. If the temperature is increased to approximately 100 °C, the rotational barriers are overcome, and the NMR spectra show only a single set of signals.

When **5e** is treated with 3-pyridinol under the standard conditions (Scheme II), no charge compensation is possible; betaine **10** is formed in high yield along with minimal O-alkylation product **11**. Under similar conditions with phenol, **12** is obtained in low yield. The cyclic amidines **15** were successfully prepared from 4-chlorobutyronitrile or 5-chlorovaleronitrile and 4-amino-3,4-dihydro-2*H*-1-benzopyran-3-ols **13** (Scheme III). The intermediate compounds **14** were not observed under the drastic reaction conditions used, and the resultant products **15a** and **15c** were subsequently acylated to afford **15b** and **15d**, respectively. To produce the 4-substituted 3,4-dihydro-2*H*-1-benzopyran compounds **17**, the alcohol **3e** was converted with PBr_3 into the bromide **16**, which then reacted with 2- or 4-pyridone (Scheme IV).

Scheme III



Scheme IV

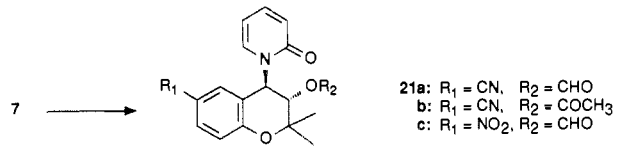


The 4-substituted 2*H*-1-benzopyran compounds **18** and **19** (Table III) were mainly prepared from the corresponding chromanol precursors **7** or **9** by brief refluxing in THF or dioxane containing solid sodium hydroxide. The amine **18f** was produced by hydrogenation of **18e** and acetylated to give **18g**. Aldehyde **18k** was obtained by transfer hydrogenation of **18a**, and thioamide **18m** was prepared by treatment of nitrile **18a** with H_2S. The ester **18j** was obtained by Pinner synthesis,[12] the amide **18u** by alkaline hydration of the nitrile **18a**.

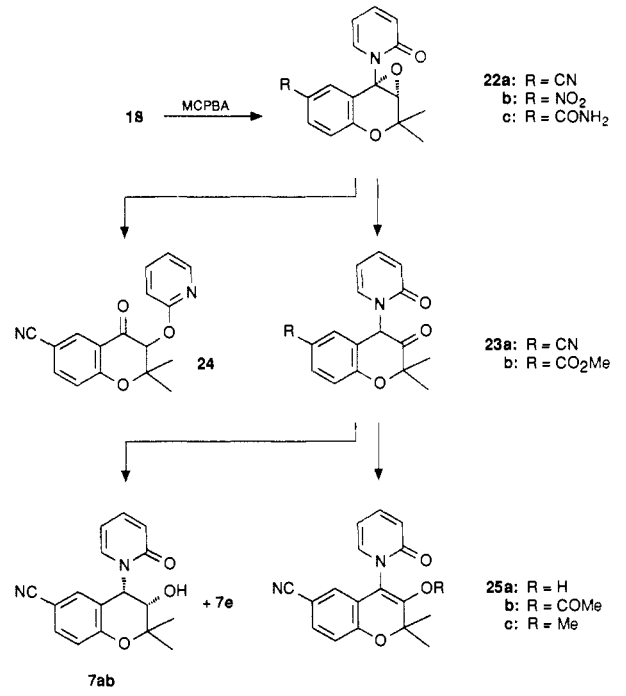
With 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (**20a**) or the corresponding 6-formyl,[2] 6-amino, or 6-carbamoyl compounds[3] as the starting material, the 6-substituted derivatives in Table IV were synthesized. The benzimidazol derivative **20c** was synthesized from aldehyde **20** (R = CHO) and 1,2-phenylenediamine.[13] The aza analogues **20b** and **20d** were synthesized from the corresponding diaminopyridines. The heterocyclic derivatives **20f**, **20j**, and **20l** were obtained by condensation of the thioamide **20e**, the amide **20** (R = $CONH_2$), or the thiourea **20k** with chloroacetone. The thioamide **20e** was obtained by addition of H_2S to nitrile **20a**, and **20k** was synthesized from amine **20** (R = NH_2) with sodium thiocyanate.[14] The Schiff bases **20g–i** were generated by condensation of the amine with the corresponding aromatic aldehydes. The addition of sodium azide to nitrile **20a** gave the tetrazol

(10) Backeberg, O. G.; Staskun, B. *J. Chem. Soc.* **1962**, 3961.
(11) Evans, R. C.; Wiselogle, F. Y. *J. Am. Chem. Soc.* **1945**, *67*, 60.
(12) Henecka, H. *Methoden der organischen Chemie* (Houben-Weyl); Georg Thieme Verlag: Stuttgart, 1952; Vol. VIII, p 536.
(13) Jonas, R.; Minck, K.; Enenkel, H.-J.; Schliep, H.-J. European Pat. 72926, 1981.
(14) Kinoshita, Y.; Matsuda, N.; Sakai, S.; Oshima, Y.; Harada, T.; Nishihara, T. *Agric. Biol. Chem.* **1966**, *30*, 447.

Scheme V



Scheme VI

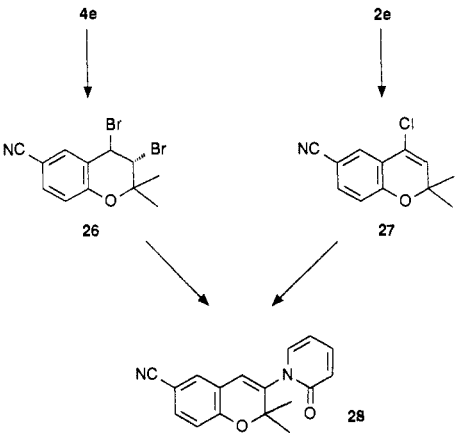


20m. The addition of methanol to **20a** under acidic conditions afforded the relatively stable imino ether **20n** as the hydrochloride, which was the intermediate product of the imidazoline derivative **20o** formed in the reaction with ethylenediamine.[15] The 4-pyridyl compound **20p** was obtained from 3,4-epoxy-3,4-dihydro-2,2-dimethyl-6-(4-pyridyl)-2*H*-1-benzopyran with 2-pyrrolidinone.

While the 3-OH group of the chromanols **7** is easily acylated (see Scheme V), it resists all attempts at oxidation to the keto compound. However, with 3-chloroperbenzoic acid, it is possible to epoxidize the chromene compounds **18** to the corresponding 3,4-epoxy compounds **22a–c** (Scheme VI). Because the epoxides are in the same oxidation state as the desired keto compounds, it was possible to convert **22a** directly to **23a** under strongly acidic conditions. It is interesting to note that the epoxide **22a** opens quite differently in the presence of a catalytic amount of tetrakis(triphenylphosphine)-palladium(0). With Pd(0), or better still with ammonia, 3,4-dihydro-2,2-dimethyl-4-oxo-3-(2-pyridyloxy)-2*H*-1-benzopyran-6-carbonitrile (**24**)[16] is obtained in a rearrangement reaction in high yield. The ketone **23b** was prepared from the nitrile **23a** by a Pinner reaction. In the reduction of the ketone **23a** with sodium borohydride, *cis*-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (**7ab**) is obtained together with the trans compound **7e** in a ratio of 1:8 (HPLC). In the NMR spectrum of **23a**, it can be seen that the ketone is to some extent in equilibrium with its enol form **25a** that can easily be converted to its acetate (**25b**) or ether (**25c**).

(15) Biedermann, J.; Leon-Lomeli, A.; Borbe, H. O.; Prop, G. *J. Med. Chem.* **1986**, *29*, 1183.
(16) Structure verified by X-ray diffraction.

Scheme VII



All attempts to obtain the chromene **18a** directly from the dibromo compound **26** or the vinyl chloride **27** by reaction with 2-pyridone failed. The attack of the nucleophile always occurred at C-3 to form the new compound **28**[16] (Scheme VII). It is assumed that a Michael-type addition took place with subsequent elimination. The dibromide **26** was generated from the chromene **4e** and the vinyl chloride **27** from the chromanone **2e** with use of phosphorus pentachloride.

Results and Discussion

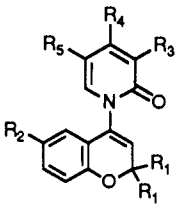
The antihypertensive effect of the compounds was determined after oral administration to conscious spontaneously hypertensive rats. Direct and indirect techniques for recording blood pressure were used.

The 4-heterocyclic substituted chroman-3-ols are listed in Tables I and II. Substitution on the 2-pyridone ring usually led to a loss of activity. The unsubstituted compounds **7e** and **7h** are highly active, the 4-methoxy-substituted **7z** shows moderate activity, while all other compounds are weakly active or inactive. The *trans*-chromanol **7e** is considerably more potent than the corresponding cis product **7ab**. In agreement with previous findings,[2] a powerful electron-withdrawing group, particularly a nitro or cyano group (**7h**, **7e**), located at C-6 is required for optimal antihypertensive activity. The methyl ketone **7f**, the methyl ester **7o**, the 4-pyridyl compound **7q**, and the vinylogous nitrile **7af** are considerably weaker. The ethyl ester **7k**, the thioamide **7x**, the aldehyde **7ac**, and the compound **7ae** are inactive.

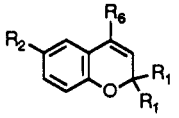
The effect of replacing the 2-pyridone group with other heterocycles is shown in Table II. Moderate blood pressure reductions were obtained with the pyridazinone compound **9f**, the corresponding partially hydrogenated compound **9g**, and the pyrazinone chromanol **9l**. Other compounds with an oxo function at the α-position in the 4-heterocycle such as pyrimidones **9i** and **9m** or the uracil derivative **9d** were either weakly active or inactive. This led us to the important question as to whether the 2-oxo function is essential to the pharmacological action in this class of substances. The change from the 2-pyridone compound **7e** to its corresponding 4-analogue **9e** resulted in a loss of activity. Further, we found the piperidinone compound **9b** inactive, while Evans et al. described the corresponding 2-analogue as strongly active.[2] The replacement of the CO group by a SO_2 group ($\rightarrow$ **9k**) also led to a reduction in activity. As mentioned, the introduction of substituents or the attachment of rings by condensation resulted in a reduction of the activity (compare **9e** with **9a**, **7e** with **9c**, **9f** with **9j** or **9n**).

A comparison of the chromene structures (Table III) with the corresponding racemic chromanols indicates that

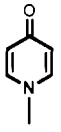
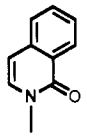
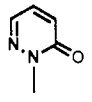
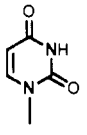
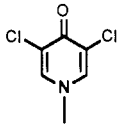
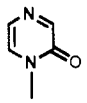
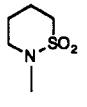
Table III. Substituted 2*H*-1-Benzopyrans 18 and 19



18



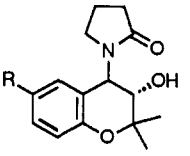
19

no.	R_1	R_2	R_3	R_4	R_5	yield, %	mp, °C	recryst solvent[a]	formula	anal.[b]	max fall[c] in BP in mmHg ± SEM in SHR
18a	Me	CN	H	H	H	85	144–146	D	$C_{17}H_{14}N_2O_2 \cdot 0.1H_2O$	C,H,N	142 ± 9
18b	Me	COMe	H	H	H	48	140–142	E	$C_{18}H_{17}NO_3 \cdot 0.3H_2O$	C,H,N	130 ± 6
18c	Me	CN	Br	H	Br	26	268–270	B	$C_{17}H_{12}Br_2N_2O_2$	C,H,Br,N	NS[d]
18d	Me	NO_2	H	H	H	24	156–158	B	$C_{16}H_{14}N_2O_4 \cdot 0.2H_2O$	C,H,N	140 ± 5
18e	Me	CN	H	H	NO_2	73	214–216	E	$C_{17}H_{13}N_3O_4 \cdot 0.5H_2O$	C,H,N	27 ± 9
18f	Me	CN	H	H	NH_2	22	177–180	G	$C_{17}H_{15}N_3O_2$	*e*	94 ± 4
18g	Me	CN	H	H	NHCOMe	26	255–256	F	$C_{19}H_{17}N_3O_3$	C,H,N	NS
18h	Me	CN	Cl	H	Cl	20	243–245	H	$C_{17}H_{12}Cl_2N_2O_2$	C,H,Cl,N	NS
18i	Me	CN	H	H	Cl	78	186–188	B	$C_{17}H_{13}ClN_2O_2$	C,H,Cl,N	23 ± 6
18j	Me	COOMe	H	H	H	61	139–141	B	$C_{18}H_{17}NO_4 \cdot 0.2H_2O$	C,H,N	98 ± 2
18k	Me	CHO	H	H	H	5	160–162	G	$C_{17}H_{15}NO_3 \cdot 0.1H_2O$	C,H,N	35 ± 3
18l	Me	4-pyridyl	H	H	H	43	174–176	E	$C_{21}H_{18}N_2O_2$	C,H,N	NS
18m	Me	$CSNH_2$	H	H	H	78	263–265	C	$C_{17}H_{18}N_2O_2S$	C,H,N,S	23 ± 9
18n	$-(CH_2)_4-$	CN	H	H	H	90	181–183	B	$C_{19}H_{18}N_2O_2$	C,H,N	26 ± 5
18o	$-(CH_2)_5-$	CN	H	H	H	81	202–204	B	$C_{20}H_{18}N_2O_2$	C,H,N	NS
18p	Me	CN	H	OBzl	H	93	211–213	F	$C_{24}H_{20}N_2O_3 \cdot 0.2H_2O$	C,H,N	NS
18q	Me	CN	H	OMe	H	57	93–95	E	$C_{18}H_{16}N_2O_3$	C,H,N	113 ± 9
18r	Me	CN	H	OEt	H	47	102–104	G	$C_{19}H_{18}N_2O_3$	C,H,N	136 ± 6
18s	$-(CH_2)_5-$	NO_2	H	H	H	59	210–212	A	$C_{19}H_{18}N_2O_4$	C,H,N	22 ± 4
18t	$-(CH_2)_4-$	NO_2	H	H	H	75	229–230	A	$C_{18}H_{16}N_2O_4$	C,H,N	NS
18u	Me	$CONH_2$	H	H	H	94	252–253	A	$C_{17}H_{16}N_2O_3 \cdot 0.3H_2O$	C,H,N	NS
18v	Me	Br	H	H	H	89	118	E	$C_{16}H_{14}BrNO_2$	C,H,Br,N	131 ± 12
19a	Me	CN	R_6 = 			47	213–214	D	$C_{17}H_{14}N_2O_2 \cdot 0.3H_2O$	C,H,N	48 ± 14
19b	Me	CN	R_6 = 			38	170–172	E	$C_{21}H_{16}N_2O_2 \cdot 0.5H_2O$	C,H,N	NS
19c	Me	CN	R_6 = 			59	136–138	G	$C_{16}H_{13}N_3O_2$	C,H,N	23 ± 11
19d	Me	CN	R_6 = 			15	278–279.5	C	$C_{16}H_{13}N_3O_3$	C,H,N	23 ± 11
19e	Me	CN	R_6 = 			25	298–299	B	$C_{17}H_{12}Cl_2N_2O_2$	C,H,Cl,N	NS
19f	Me	CN	R_6 = 			36	136–138	E	$C_{16}H_{13}N_3O_2 \cdot 0.2H_2O$	C,H,N	105 ± 7
19g	Me	CN	R_6 = 			26	175	E	$C_{16}H_{18}N_2O_3S \cdot 0.2H_2O$	C,H,N,S	25 ± 5

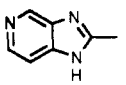
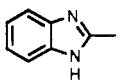
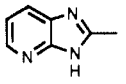
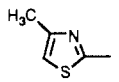
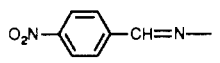
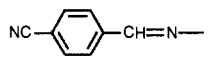
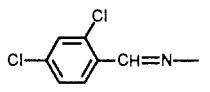
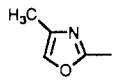
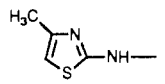
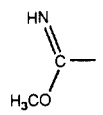
[a–d] See footnotes in Table I. [e] Consistent analyses could not be obtained. $C_{17}H_{15}N_3O_2$ found *m/z* 293.1164, calcd 293.1164 (MS).

the antihypertensive action of the chromenes was significantly stronger in most cases. This applies to the 4-(1,2-dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyrans with substituents at C-6 such as nitriles (**7e** → **18a**), the methyl ketones (**7f** → **18b**), the nitro compounds (**7h** → **18d**), the methyl esters (**7o** → **18j**), and the brominated compounds (**7ag** → **18v**). Among the highly active compounds in Table III, there are some in which the 2-pyridone group

Table IV. 6-Substituted 3,4-Dihydro-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-3-ols **20**



20

no.	R	yield, %	mp, °C	recryst solvent	formula	anal.[b]	max fall[c] in BP in mmHg ± SEM in SHR
20a	CN (Cromakalim)				$C_{16}H_{18}N_2O_3$		78 ± 6
20b		53	>310	Me_2CHOH	$C_{21}H_{22}N_4O_3 \cdot 0.1H_2O$	C,H,N	NS[d]
20c		42	218–220	H_2O	$C_{22}H_{23}N_3O_3 \cdot 0.9H_2O$	C,H,N	NS
20d		43	230	MeOH	$C_{21}H_{22}N_4O_3 \cdot 0.6H_2O$	C,H,N	NS
20e	H_2NCS-	83	234–236	MeOH	$C_{16}H_{20}N_2O_3S \cdot 0.5H_2O$	C,H,N,S	22 ± 7
20f		76	220–223	EtOH	$C_{19}H_{22}N_2O_3S \cdot HCl$	C,H,Cl,N,S	NS
20g		92	250–252	EtOH	$C_{22}H_{23}N_3O_5$	C,H,N	26 ± 7
20h		71	285–287	EtOH	$C_{23}H_{23}N_3O_3$	C,H,N	NS
20i		81	225–226	EtOH	$C_{22}H_{22}Cl_2N_2O_3$	C,H,Cl,N	NS
20j		64	208–210	EtOAc	$C_{19}H_{22}N_2O_4$	C,H,N	NS
20k	H_2NCSNH-	93	235–237	MeOH	$C_{16}H_{21}N_3O_3S$	C,H,N,S	NS
20l		49	255	EtOH	$C_{19}H_{23}N_3O_3S$	C,H,N,S	NS
20m		75	296–297	H_2O	$C_{16}H_{19}N_5O_3$	C,H,N	NS
20n		80	164–166	MeOH	$C_{17}H_{22}N_2O_4 \cdot 2HCl$	C,H,Cl,N	76 ± 5
20o		98	202–206	Me_2CHOH	$C_{18}H_{23}N_3O_3$	C,H,N	NS
20p	4-pyridyl	24	238–239	EtOH	$C_{20}H_{22}N_2O_3$	C,H,N	20 ± 3

[b–d] See footnotes in Table I.

is substituted such as the 5-amino compound **18f** and the 4-methoxy and 4-ethoxy derivatives **18q** and **18r**, which should be compared with **7n**, **7z**, or **7aa**. As in the chromanol series, however, all the substituted compounds were weaker than **18a**. It should still be mentioned that the influence of C-6 substituents in the pyridone ring could not be investigated as these substances have not been accessible by synthesis so far. The pyrazinone derivative **19f** was found to be more active than alcohol **9l** but less than the pyridone derivative **18a**. The spirocyclic compounds **7a–d**, **18n**, **18o**, **18s**, and **18t** showed only token activity in their chromene form. The reason for the increase in potency with the change from the chromanols to the chromenes, which was in some cases extreme (**7aa** → **18r**, **7ag** → **18v**), is still unclear. A series of exceptions (**7m**, **7q**, **9c**, **9f**, **9k** vs **18i**, **18l**, **19b**, **19c**, **19g**) to the trend described made an explanation even more difficult.

The attempt to exceed the potency of **20a** by replacing the nitrile group with new substituents, particularly with heterocyclic groups, met with little success (Table IV). Only the imino ether **20n** showed hypotensive action similar to that of Cromakalim. All the other compounds were either only weakly effective (**20e**, **20g**, **20p**) or inactive altogether. Replacement of the oxo function in **20a** by an imino function (**15a**) surprisingly resulted in complete loss of activity. This also applied to the analogues **15b–e** (Scheme III, Table V). Also inactive were the products with oxygen at C-4 (chromanols **8**, **11**, and **12**; Schemes I, II), which were formed in small quantities, as well as the betaine **10**.

Table V. Compounds of Schemes III–VI

no.	yield, %	mp, °C	recryst solvent	formula	anal.[b]	max fall[c] in BP in mmHg ± SEM in SHR
15c	5	287	H_2O	$C_{17}H_{21}N_3O_2 \cdot HCl$	C,H,Cl,N	NS[d]
15d	51	178–180	Et_2O	$C_{22}H_{22}N_4O_3$	C,H,N	NS
15e	23	>295	MeOH	$C_{15}H_{19}N_3O_4 \cdot HCl$	C,H,Cl,N	NS
17a	4	157–159	Et_2O	$C_{17}H_{16}N_2O_2$	C,H,N	92 ± 11
17b	11	141–142	EtOAc	$C_{17}H_{16}N_2O_2 \cdot 0.2H_2O$	C,H,N	NS
21a	49	203.5–204	EtOAc	$C_{18}H_{16}N_2O_4 \cdot 0.1H_2O$	C,H,N	101 ± 6
21b	82	228–228.5	EtOH	$C_{19}H_{18}N_2O_4$	C,H,N	89 ± 15
21c	32	193	Et_2O	$C_{17}H_{16}N_2O_6$	C,H,N	129 ± 3
22a	54	128–131	Et_2O	$C_{17}H_{14}N_2O_3 \cdot 0.1H_2O$	C,H,N	69 ± 6
22b	43	132	Et_2O	$C_{16}H_{14}N_2O_5$	C,H,N	118 ± 11
22c	40	162–164	Et_2O	$C_{17}H_{16}N_2O_4$	C,H,N	NS
23a	88	175–178	Me_2CHOH	$C_{17}H_{14}N_2O_3 \cdot 0.1H_2O$	C,H,N	20 ± 8
23b	20	137–139	Et_2O	$C_{18}H_{17}NO_5$	C,H,N	NS
25b	35	158–160	Et_2O	$C_{19}H_{16}N_2O_4 \cdot 0.3H_2O$	C,H,N	21 ± 6
25c	60	186–188	Et_2O	$C_{18}H_{16}N_2O_3 \cdot 0.2H_2O$	C,H,N	22 ± 7

[b–d] See footnotes in Table I.

Removal of the 3-hydroxy group from the chromane system resulted in a slightly less potent compound (**17a**). After esterification of the hydroxy group with short-chain acids (Scheme V) high potency was retained particularly with the formates (compare **21a** with **7e** and **21c** with **7h**), while in the case of the acetate **21b** a reduction was observed. The epoxides **22a** and **22b** also possess good activity, the nitro compound **22b** being equivalent in its potency even to the corresponding highly potent alcohol **7h** (Scheme VI, Table V). It is therefore surprising to find that the ketone **23a** along with its tautomeric form **25a**, obtained by isomerization from **22a**, lost practically all of their potency. The activity of the enforced enol forms (**25b**, **25c**) remained at the same low level. The new structure **24** was inactive.

Antihypertensive ED_{30} values were used to compare the relative potencies of selected compounds (Table VI). The group of the chromenes contains the most active compounds, with 4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (**18d**) [ED_{30} = 0.83 μg/kg] being the most potent, which promises to be one of the most active of all hypotensive substances known to date. This is followed in potency by the corresponding nitrile **18a**, the methyl ketone **18b**, the compound **18r** substituted with an ethoxy group in the pyridone ring, and the pyrazinone derivative **19f**. However, the group of the chromanols also contains substances with remarkable ED_{30} values such as pyrazinone **9l**, the nitro compound **7h**, and the formate **21a**. All of these compounds are far superior in potency to Cromakalim (**20a**). Substances with particularly shallow dose/response curves are the chromanols **9l** and **9f**, while the brominated compound **18v** has a steeper curve. The ratio ED_{30} (20 h)/ED_{30} (2 h) gives a reference to the period of activity of the individual substances. We found that the most potent substance **18d** has the shortest period of activity while, for instance, the pyridazinone compounds **9f** and **9g** demonstrate prolonged activity.

The new group of benzopyran derivatives belongs to the class of compounds modulating the potassium channels. Similar to the other substances in this class,[1] they possess the ability to hyperpolarize smooth muscle cell membranes.[17,18] The hyperpolarization is responsible for the relaxant effects in the smooth muscle and thus also for vasodilation. Thus it is not surprising that the relative potencies in hyperpolarization, relaxation, and antihypertension of the individual substances are approximately similar.

Table VI. Comparative Hypotensive Effects of Selected Compounds following Oral Administration to Conscious SHR

no.	ED_{30},[a] μg/kg	ED_{30} (2 h),[b] μg/kg	ED_{30} (20 h),[b] μg/kg	ED_{30} (20 h) / ED_{30} (2 h)
7e	50	45	138	3.1
7h	24	35	884	25.2
7z	197	NT[c]	NT	–
9f	36	45	82	1.8
9g	211	56	148	2.6
9l	10	291	1290	4.4
17a	150	NT	NT	–
18a	10	36	186	5.2
18b	25	74	546	7.4
18d	0.83	0.7	102	145.7
18f	206	341	1609	4.7
18j	202	573	2063	3.6
18q	66	NT	NT	–
18r	17	137	>1000	>7.3
18v	110	69	1271	18.4
19f	22	38	357	9.4
20n	83	NT	NT	–
21a	30	67	416	6.2
21b	106	112	405	3.6
21c	74	NT	NT	–
22a	202	NT	NT	–
22b	60	NT	NT	–
20a	110	131	603	4.6

[a] Mean blood pressure; dose required to reduce blood pressure by 30 mmHg. [b] Systolic blood pressure was measured 2 and 20 h after administration. [c] Not tested.

In further studies[19] hypotensive and nonhypotensive doses of 4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (**18a** = EMD 52 692) showed potent coronary artery dilation in vivo. Gross et al.[20] were able to show that in anesthetized dogs subjected to an acute coronary artery occlusion, the collateral blood flow in the ischemic area was increased by low doses of **18a**, which influenced neither the circulation in the nonischemic

(17) de Peyer, J.-E.; Lues, I.; Gericke, R.; Häusler, G. Presented as poster at the 6th International Round Table: K^+ Channels, Paris, 1989.

(18) Gericke, R.; Lues, I.; de Peyer, J.-E.; Häusler, G. Presented at the 30th Spring Meeting, German Society Pharmacology and Toxicology, Mainz, 1989: *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, Suppl 339, Abstr 247.

(19) Schliep, H.-J.; Becker, K.-H.; Bergmann, R.; Haase, A. F.; Schelling, P.; Schulze, E. Presented at the 30th Spring Meeting, German Society Pharmacology and Toxicology, Mainz, 1989: *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, Suppl 339, Abstr 248.

(20) Maruyama, M.; Farber, N.; Gross, G. J. Presented at the FASEB, 73rd Annual Meeting, New Orleans, 1989, Abstr 3894.

regions of the heart nor the blood pressure. For this reason, the development of **18a** as a coronary vasodilator and antianginal drug has been initiated.

Experimental Section

Melting points were determined with a Büchi 535 melting point apparatus and are uncorrected. IR, NMR, and mass spectra, which were in agreement with the structures cited, were recorded on a Bruker 85 FT-IR spectrometer, a Bruker AC 200 or WM 250 (TMS as internal standard), and a Vacuum Generators VG 70-70 or 70-250 at 70 eV, respectively. Elemental analyses were conducted with a Perkin-Elmer-240 B-CHN analyzer. Precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from E. Merck, Darmstadt were used for thin-layer chromatography. Yields are not optimized.

3′,4′-Dihydro-4′-oxospiro[cyclohexane-1,2′-[2*H*][1]benzopyran]-6′-carbonitrile (2c). 3-Acetyl-4-hydroxybenzonitrile (37.5 g, 0.23 mol), cyclohexanone (29 g, 0.3 mol), and pyrrolidine (5 mL, 60 mmol) were refluxed in absolute PhMe (180 mL) for 2 h with a Dean–Stark apparatus. The solvent was evaporated and the residue purified by chromatography (silica gel, CH_2Cl_2). The homogeneous fractions were combined (50.5 g, 90%) and a part recrystallized from $(Me_2CH)_2O$: mp 92–94 °C; NMR (DMSO-d_6) δ 1.6 (m, 8 H), 1.9 (m, 2 H), 2.89 (s, 2 H), 7.23 (d, 8.8, 1 H), 7.96 (dd, 8.8, 1.7, 1 H), 8.10 (d, 1.7, 1 H). Anal. ($C_{15}H_{15}NO_2$) C, H, N.

Spiro[cyclohexane-1,2′-[2*H*][1]benzopyran]-6′-carbonitrile (4c). Ketone **2c** (50.5 g, 0.21 mol) in MeOH (800 mL) was reduced with $NaBH_4$ (11 g, 0.29 mol). The solvent was evaporated, and the residue was taken up in H_2O (300 mL) and extracted three times with Et_2O. The combined ether extracts were dried and evaporated, yielding a gum consisting of 3′,4′-dihydro-4′-hydroxyspiro[cyclohexane-1,2′-[2*H*][1]benzopyran]-6′-carbonitrile (**3c**), 50 g (98%). The crude **3c** (50 g, 0.21 mol) and *p*-toluenesulfonic acid hydrate (2.2 g, 11.6 mmol) were refluxed in PhMe (700 mL) for 4 h with a Dean–Stark apparatus. The solvent was evaporated and the residue crystallized from Me_2CHOH to yield **4c**: 36 g (78%); mp 94–95 °C; NMR (DMSO-d_6) δ 1.6 (m, 8 H), 1.8 (m, 2 H), 5.90 (d, 10.2, 1 H), 6.47 (d, 10.2, 1 H), 6.92 (d, 8.4, 1 H), 7.56 (m, 2 H). Anal. ($C_{15}H_{15}NO$) C, H, N.

3′,4′-Epoxy-3′,4′-dihydrospiro[cyclohexane-1,2′-[2*H*][1]benzopyran]-6′-carbonitrile (5c). 3-Chloroperbenzoic acid (85%; 12.5 g, 61.6 mmol) dissolved in CH_2Cl_2 (80 mL) was added dropwise to a solution of **4c** (13.5 g, 60 mmol) in CH_2Cl_2 (100 mL) at 5 °C. After the mixture was stirred overnight at room temperature, a precipitate was filtered off. The remaining solution was evaporated and the residue purified by chromatography (silica gel, CH_2Cl_2/petroleum ether, 75:25), affording 8.5 g (59%) of **5c**: mp 54–56 °C; NMR ($CDCl_3$) δ 1.3–1.9 (m, 10 H), 3.55 (d, 4, 1 H), 3.89 (d, 4, 1 H), 6.91 (d, 7.7, 1 H), 7.54 (dd, 7.7, 1.7, 1 H), 7.65 (d, 1.7, 1 H). Anal. ($C_{15}H_{15}NO_2$) C, H, N.

General Procedure for Compounds of Tables I and II. 3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (7e). The epoxide **5e** (30 g, 0.15 mol), 2-pyridone (22 g, 0.23 mol), and pyridine (10 mL, 0.12 mol) were heated in refluxing EtOH (100 mL) for 2 h. After cooling, **7e** (27 g, 61%) was collected by filtration: mp 245–246 °C from Me_2CHOH; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.49 (s, 3 H), 3.82 (dd, 10.2, 4.9, 1 H), 4.15 (d, 4.9, 1 H), 6.23 (td, 7.4, 1.7, 1 H), 6.35 (d, 10.2, 1 H), 6.63 (d, 7.4, 1 H), 6.87 (dd, 7.4, 1.7, 1 H), 6.95 (d, 8.4, 1 H), 7.06 (s br, 1 H), 7.40 (td, 7.4, 1.7, 1 H), 7.47 (dd, 8.4, 1.7, 1 H). Anal. ($C_{17}H_{16}N_2O_3$) C, H, N. The mother liquor was evaporated and the residue chromatographed (silica gel, Et_2O/EtOAc, 1:1), yielding 11.5 g (26%) of oily 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(2-pyridyloxy)-2*H*-1-benzopyan-6-carbonitrile (**8**, R_1 = Me, R_2 = CN, R_3–R_5 = H), which crystallized after standing for some time: mp 102–103 °C from $(Me_2CH)_2O$; NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.58 (s, 3 H), 3.95 (d, 7.7, 1 H), 5.79 (d, 7.7, 1 H), 6.49 (s br, 1 H), 6.90 (d, 8.4, 1 H), 7.00 (d, 7.7, 1 H), 7.05 (dd, 4.9, 1.5, 1 H), 7.49 (dd, 7.7, 1.7, 1 H), 7.69 (s br, 1 H), 7.75 (td, 7.7, 1.7, 1 H), 8.15 (dd, 4.9, 1.5, 1 H). Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

***trans*-4-(3-Amino-1,2-dihydro-2-oxo-1-pyridyl)-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (7p).** The nitro compound **7j** (1 g, 2.9 mmol) was hydrogenated in MeOH (50 mL) with Pd/C (5% Pd; 500 mg). The catalyst was filtered off and **7p** (440 mg, 47%) was obtained as a crystalline solid after evaporation; mp 213–215 °C. Anal. ($C_{17}H_{17}N_3O_3 \cdot 0.6H_2O$) C, H, N.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbothioamide (7x).** H_2S was passed through a solution of **7e** (2 g, 6.7 mmol) in pyridine (12 mL) and NEt_3 (6 mL) at 130 °C for 12 h. The solvents were distilled off, and the residue was crystallized from MeOH/EtOAc, 1:1. This yielded 1.4 g (61%) of **7x**, mp 226–228 °C (MeOH). Anal. ($C_{17}H_{18}N_2O_3S \cdot 0.5H_2O$) C, H, N, S.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbaldehyde (7ac).** Compound **7e** (1 g, 3.4 mmol), sodium hypophosphite hydrate (2 g, 11.4 mmol), and Raney nickel (400 mg) were stirred in a mixture of H_2O (10 mL), acetic acid (10 mL), and pyridine (20 mL) at 40–45 °C for 6 h. The catalyst was removed, and H_2O (100 mL) was added to the filtrate. The solution was extracted with Et_2O; the Et_2O phase was evaporated and the residue chromatographed (silica gel; $Et_2O \rightarrow$ EtOAc). The homogeneous fractions were combined to give 200 mg (20%): mp 222–224 °C; NMR (DMSO-d_6, 90 °C) δ 1.29 (s, 3 H), 1.50 (s, 3 H), 4.17 (d, 9.5, 1 H), 5.79 (s br, 1 H), 6.19 (td, 6.5, 1.0, 1 H), 6.41 (d, 8.5, 1 H), 6.93 (d, 7.7, 1 H), 7.17 (d, 1.0, 1 H), 7.31–7.40 (m, 3 H), 7.65 (dd, 7.7, 1.0, 1 H), 9.7 (s, 1 H). Anal. ($C_{17}H_{17}NO_4 \cdot 0.2H_2O$) C, H, N.

3-[*trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-yl]acrylonitrile (7af). Under N_2, NaH (80%, 300 mg, 10 mmol) was added to diglyme (4 mL), and then diethyl (cyanomethyl)phosphonate (600 mg, 3.4 mmol) followed by aldehyde **7ac** (1 g, 3.3 mmol) dissolved in diglyme (3 mL) was added dropwise, and the mixture was stirred for 3 h at room temperature. The solution was poured into H_2O (50 mL) and extracted three times with EtOAc (30-mL portions). The combined organic phase was dried and evaporated. The residue was eluted through a silica gel column ($Et_2O \rightarrow$ EtOAc); the chromatographically homogeneous fractions were combined and crystallized from Et_2O. **7af**: yield 130 mg (12%); mp 190–192 °C; NMR (DMSO-d_6 + CF_3CO_2D, 90 °C) δ 1.29 (s, 3 H), 1.49 (s, 3 H), 4.14 (d, 9.5 1 H), 5.82 (s br, 1 H), 5.91 (dd, 15.5, 1.0, 1 H), 6.25 (td, 6.0, 1.0, 1 H), 6.50 (d, 9.0, 1 H), 6.90 (m, 2 H), 7.32–7.52 (m, 4 H). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(4-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-carbonitrile (9b).** Epoxide **5e** (1 g, 5 mmol), 4-piperidone hydrate hydrochloride (480 mg, 5.5 mmol), and Et_3N (1.4 mL, 10.1 mmol) were heated at reflux in EtOH (10 mL) for 2 days. The reaction mixture was evaporated, and the residue was redissolved in CH_2Cl_2 and washed twice with H_2O. After drying, the organic phase was evaporated and chromatographed (silica gel, petroleum ether $\rightarrow$ Et_2O) to yield 170 mg (11%) of **9b**: mp 142–145 °C; NMR (DMSO-d_6) δ 1.15 (s, 3 H), 1.41 (s, 3 H), 2.4 (m, 4 H), 3.0 (m, 4 H), 3.75 (dd, 10, 6.8, 1 H), 3.89 (d, 10, 1 H), 5.59 (d, 6.8, 1 H), 6.91 (d, 8.0, 1 H), 7.61 (dd, 8.0, 1.6, 1 H), 8.15 (d, 1.6, 1 H). Anal. ($C_{17}H_{20}N_2O_3$) C, H, N.

***trans*-3,4-Dihydro-4-(1,4,5,6-tetrahydro-6-oxo-1-pyridazinyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (9g).** Epoxide **5e** (13 g, 65 mmol), 1,4,5,6-tetrahydropyridazin-6-one (6.5 g, 66.2 mmol), and NaH (80%; 1.95 g, 65 mmol) were stirred in DMSO (200 mL) for 2 h at room temperature under N_2 atmosphere. The reaction mixture was then poured into H_2O (1 L) and the aqueous solution was extracted twice with CH_2Cl_2 (500 mL). The organic phase was washed with H_2O, dried, evaporated, and chromatographed (silica gel, CH_2Cl_2 $\rightarrow$ EtOAc); the chromatographically homogeneous fractions were combined. **9g**: yield 1.3 g (7%); mp 163–165 °C; NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.47 (s, 3 H), 2.5–2.8 (m, 4 H), 2.75 (d, 6.7, 1 H), 4.02 (dd, 9.8, 6.7, 1 H), 5.75 (d, 9.8, 1 H), 6.84 (d, 8.8, 1 H), 7.14 (m, 1 H), 7.24 (d, 2.8, 1 H), 7.39 (dd, 8.8, 2.8, 1 H). Anal. ($C_{16}H_{17}N_3O_3$) C, H, N.

***trans*-3,4-Dihydro-4-(1,4-dihydro-4-oxo-1-pyrimidinyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (9h) and *trans*-3,4-Dihydro-4-(1,6-dihydro-6-oxo-1-pyrimidinyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (9i).** Epoxide **5e** (6 g, 29.8 mmol), pyrimidin-4-ol (4.4 g, 45.8 mmol), and pyridine (2.2 mL, 27.3 mmol) were heated at reflux in EtOH (200 mL) for 6 h. The hot solution was filtered and

evaporated, and the residue was chromatographed (silica gel, CH_2Cl_2 → MeOH), giving **9i** followed by **9h**. **9h**: yield 1.43 g (16%); mp 307–310 °C; NMR (DMSO-d_6) δ 1.21 (s, 3 H), 1.46 (s, 3 H), 3.86 (m, 10, 6.1, 1 H), 5.17 (d, 10, 1 H), 6.02 (d, 7.7, 1 H), 6.16 (d, 6.1, 1 H), 7.03 (d, 8.5, 1 H), 7.52 (d, 2.0, 1 H), 7.56 (dd, 7.7, 2.7, 1 H), 7.69 (dd, 8.5, 2.1, 1 H), 8.39 (d, 2.7, 1 H). Anal. ($C_{16}H_{15}N_3O_3$) C, H, N.

9i: yield 1.88 g (21%); mp 207–208 °C; NMR (DMSO-d_6, 390 K) δ 1.24 (s, 3 H), 1.48 (s, 3 H), 4.26 (d, 9.8, 1 H), 5.39 (d, 9.8, 1 H), 6.34 (d, 6.6, 1 H), 6.94 (d, 8.5, 1 H), 7.17 (m, 1 H), 7.52 (dd, 8.5, 2.3, 1 H), 7.89 (d, 6.6, 1 H), 8.34 (s **br**, 1 H). Anal. ($C_{16}H_{15}N_3O_3$) C, H, N.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyrimidinyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (9m).** Na (460 mg, 20 mmol) followed by pyrimidin-2-ol hydrochloride (2.6 g, 19.6 mmol) were placed in EtOH (100 mL) under N_2. The solution was heated to boiling and the epoxide **5e** (4 g, 19.9 mmol) added and refluxing continued for 6 h. The hot mixture was then filtered, and the crystals were separated from the cooled solution (4 g, 68%), mp 252–253 °C. Anal. ($C_{16}H_{15}N_3O_3$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(3-oxidopyridinio)-2*H*-1-benzopyran-6-carbonitrile (10) and *trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(3-pyridyloxy)-2*H*-1-benzopyran-6-carbonitrile (11).** The epoxide **5e** (6 g, 29.8 mmol), 3-pyridinol (3 g, 31.5 mmol), and pyridine (3 mL, 37.2 mmol) were heated at reflux for 4 h in EtOH (120 mL). The solution was reduced to half the volume and cooled. The precipitated crystals **10** were isolated, yield 6.5 g (74%). A portion was recrystallized from MeOH/3% H_2O: mp 196–199 °C; NMR (DMSO-d_6 + TFA), δ 1.28 (s, 3 H), 1.52 (s, 3 H), 4.16 (d, 9.8, 1 H), 5.94 (d, 9.8, 1 H), 7.12 (d, 8.4, 1 H), 7.53 (s **br**, 1 H), 7.76 (dd, 8.4, 1.7, 1 H), 7.92–8.14 (m, 2 H), 8.40–8.80 (d **br**, 2 H). Anal. ($C_{17}H_{16}N_2O_3 \cdot 0.5H_2O$) C, H, N. The mother liquor was evaporated to a residue and chromatographed (silica gel, EtOAc → MeOH), and the chromatographically homogeneous fractions of substance **11** were combined; yield 1.2 g (14%). A part was recrystallized from EtOAc: mp 204–206 °C; NMR (DMSO-d_6) δ 1.32 (s, 3 H), 1.4 (s, 3 H), 3.80 (m, 1 H), 5.40 (d, 6.3, 1 H), 5.94 (d, 6.0, 1 H), 6.99 (d, 8.1, 1 H), 7.41 (dd, 8.1, 4.2, 1 H), 7.60–7.80 (m, 3 H), 8.26 (d **br**, 4.2, 1 H), 8.51 (d br, 2.8, 1 H). Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-phenoxy-2*H*-1-benzopyran-6-carbonitrile (12).** Epoxide **5e** (2 g, 9.9 mmol), PhOH (1 g, 10.6 mmol), and pyridine (1.6 mL, 19.8 mmol) were heated at reflux for 5 h in EtOH (20 mL). The solvent was evaporated and the residue chromatographed (silica gel, petroleum ether 50–70 °C → Et_2O). This was further purified by chromatography through a Lobar prepacked column, size C, LiChroprep St 60, 40–63 μm (Merck), using petroleum ether/Et_2O 1:1. The homogeneous fractions were combined to yield 400 mg (14%) of **12**: mp 97.5–99 °C; NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.46 (s, 3 H), 2.28 (d, 5.3, 1 H), 3.91 (dd, 7.0, 5.3, 1 H), 5.23 (d, 7.0, 1 H), 6.8 (d, 8.8, 1 H), 6.99–7.41 (m, 5 H), 7.46 (dd, 8.8, 1.7, 1 H), 7.60 (d, 1.7, 1 H). Anal. ($C_{18}H_{17}NO_3$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-4-(2-imino-1-pyrrolidinyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (15a).** Compound **13**[21] (R_1 = CN; 10.6 g, 48.6 mmol), Et_3N (15 mL, 108.2 mmol), and 4-chlorobutyronitrile (8 mL, 84.2 mmol) were heated to 130 °C for 3 h in a small flask. After cooling, the melt was recrystallized from MeCN (ca. 50 mL). The precipitate was separated and dissolved in H_2O and the base precipitated by addition of NaOH. **15a**: yield 5 g (36%); mp 205–206 °C; NMR (DMSO-d_6) δ 1.20 (s, 3 H), 1.45 (s, 3 H), 1.89 (m, 2 H), 2.50 (m, 2 H), 2.89 (m, 1 H), 3.30 (m, 1 H), 3.75 (d, 10, 1 H), 5.15 (d, 10, 1 H), 6.02 (s **br**, 2 H), 6.91 (d, 8.4, 1 H), 7.31 (d, 1.9, 1 H), 7.59 (dd, 8.4, 1.9, 1 H). Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

***trans*-4-[2-(Benzoylimino)-1-pyrrolidinyl]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (15b).** Compound **15a** (200 mg, 0.7 mmol) and Et_3N (0.5 mL, 3.6 mmol) were dissolved in absolute THF (10 mL), mixed with benzoyl chloride (0.3 mL, 2.6 mmol), and stirred at room temperature for 2 h. The precipitate was collected and discarded. The mother liquor was evaporated and the residue chromatographed on a silica gel column (Et_2O → EtOAc). The chromatographically homogeneous fractions were combined and crystallized from Et_2O/petroleum ether 1:1, yield 240 mg (88%). A part was recrystallized from EtOAc: mp 230–232 °C; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.59 (s, 3 H), 2.08 (q, 7, 2 H), 3.27 (m, 4 H), 4.01 (s br, 1 H), 4.54 (s br, 1 H), 5.86 (s br, 1 H), 6.97 (d, 10, 1 H), 7.35 (s, 1 H), 7.40 (t, 9, 1 H), 7.50 (t, 9, 2 H), 8.09 (br, 3 H). Anal. ($C_{23}H_{23}N_3O_3$) C, H, N.

4-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (16). 3,4-Dihydro-4-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (**3e**), prepared as described under **3c** (46 g, 226 mmol), was dissolved in absolute PhMe (500 mL) after which PBr_3 (11.5 mL, 123 mmol) was added and the mixture stirred overnight at room temperature. The solvent was evaporated off, and the residue was dissolved in EtOAc and extracted twice with H_2O (200 mL each time). The organic phase was dried and evaporated, and the residue was filtered through a silica gel column (petroleum ether → Et_2O): yield 43 g (71%); mp 89–92 °C; NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.52 (s, 3 H), 2.40 (dd, 14.1, 8.4, 1 H), 2.50 (dd, 14.1, 6.7, 1 H), 5.35 (dd, 8.4, 6.7, 1 H), 6.81 (d, 8.5, 1 H), 7.43 (dd, 8.5, 1 H), 7.86 (d, 1, 1 H). Anal. ($C_{12}H_{12}BrNO$) C, H, Br, N.

3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (17a). Compound **16** (10 g, 37.6 mmol) and 2-pyridone (6.3 g, 66.2 mmol) were dissolved in DMSO, and NaH (80%, 1.2 g, 40 mmol) was added. The mixture was stirred for 3 days, poured into H_2O (1 L), and extracted three times with EtOAc (500 mL each time); the organic phases were combined and dried, evaporated, and chromatographed through a silica gel column using Et_2O. The chromatographically homogeneous fractions were combined: yield 430 mg (4.1%): mp 157–159 °C; NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.52 (s, 3 H), 1.94 (m, 1 H), 2.32 (dd, 13.4, 6.3, 1 H), 6.20 (td, 6.7, 0.5, 1 H), 6.52 (m, 1 H), 6.67 (d, 9.1, 1 H), 6.94 (d, 8.1, 2 H), 7.11 (s br, 1 H), 7.36 (ddd, 7.7, 7.4, 1.7, 1 H), 7.46 (dd, 8.4, 0.7, 1 H). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

General Procedure for Compounds 18 and 19. 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (18a). Chromanol **7e** (100 g, 337 mmol) and NaOH on a carrier (0.8–1.6 mm, ~14–25 mesh ASTM; Cat. No. 1567, E. Merck; 100 g) were heated at reflux in dioxane (3 L) in a stream of N_2 for 10 min. The solution was filtered and evaporated, and the residue was dissolved in CH_2Cl_2 (1 L) and washed twice with H_2O (500 mL each time). The organic phase was dried and evaporated, and the residue recrystallized from $(Me_2CH)_2O$ (500 mL) to give 80 g (85%) of **18a**. A part was recrystallized from Me_2CHOH: mp 144–146 °C; NMR ($CDCl_3$) δ 1.50 (s, 3 H), 1.65 (s, 3 H), 5.80 (s, 1 H), 6.27 (td, 6, 0.7, 1 H), 6.64 (d, 9.9, 1 H), 6.90 (d, 8.8, 1 H), 6.94 (d, 1.7, 1 H), 7.17 (dd, 6.3, 1.7, 1 H), 7.42 (dd, 9.9, 1.7, 1 H), 7.47 (td, 6.3, 1.4, 1 H). Anal. ($C_{17}H_{14}N_2O_2 \cdot 0.1H_2O$) C, H, N.

4-(5-Acetamido-1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (18g). Nitro compound **18e** (1.5 g, 4.6 mmol) was hydrogenated in MeOH (25 mL) with Pd/C (5% Pd; 200 mg) until no further H_2 was absorbed. The catalyst was filtered off and the solution evaporated. The crude amine **18f** was treated for 2 h with Ac_2O (3 mL, 31.7 mmol) and pyridine (3 mL, 37.2 mmol). The solution was evaporated to a residue which was chromatographed on a silica gel column (EtOAc → MeOH). The homogeneous fractions were recrystallized from MeCN to give 400 mg (26%) of **18g**: mp 255–256 °C; NMR ($CDCl_3$) δ 1.54 (s, 3 H), 1.60 (s, 3 H), 2.10 (s, 3 H), 5.83 (s, 1 H), 6.57 (d, 10.2, 1 H), 6.89 (d, 8.1, 1 H), 6.92 (d, 1, 1 H), 7.44 (m, 2 H), 8.17 (d, 2.4, 1 H), 9.32 (s br, 1 H). Anal. ($C_{19}H_{17}N_3O_3$) C, H, N.

Methyl 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carboxylate (18j). HCl gas was passed into a boiling solution of nitrile **18a** (15 g, 53.9 mmol) in MeOH (150 mL) for 4.5 h. The solution was left to stand overnight, after which time the solvent was distilled off and H_2O (150 mL) added to the residue which was then heated for 1 h on a steam bath. The water was decanted off, the residue dissolved in CH_2Cl_2 and chromatographed on a silica gel column (CH_2Cl_2/EtOAc 1:1) to yield 10.2 g (60%) of **18j**: mp 139–141 °C; NMR ($CDCl_3$) δ 1.48 (s, 3 H), 1.54 (s, 3 H), 3.75 (s, 3 H), 5.71 (s, 1 H), 6.21 (td, 6.7, 0.7, 1 H),

(21) Evans, J. M.; Buckingham, R. E.; Willcocks, K. Eur. Pat. Appl. EP 76075, 1983.

6.62 (d, 9.5, 1 H), 6.84 (d, 7.7, 1 H), 7.15 (dd, 6.5, 1 H), 7.34 (d, 1.4, 1 H), 7.44 (dd, 7.4, 1, 1 H), 7.86 (dd, 9.5, 1.4, 1 H). Anal. ($C_{18}H_{17}NO_4 \cdot 0.2H_2O$) C, H, N.

4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carboxamide (18u). Nitrile **18a** (7 g, 25.2 mmol) and KOH (14 g, 250 mmol) were heated at reflux for 50 min in *tert*-butyl alcohol (100 mL). After cooling, H_2O (1 L) was added, and the mixture was extracted with EtOAc. The solution was dried and evaporated, and the residue was recrystallized from EtOH to yield 7 g (92%) of **18u**: mp 252–253 °C; NMR (DMSO-d_6) δ 1.48 (s, 3 H), 1.52 (s, 3 H), 6.00 (s, 1 H), 6.34 (td, 6.7, 0.5, 1 H), 6.47 (d, 8.8, 1 H), 6.89 (d, 7.8, 1 H), 7.14 (d, 1, 1 H), 7.15 (s br, 1 H), 7.54 (d, 6.9, 1 H), 7.57 (td, 7.8, 1, 1 H), 7.74 (dd, 7.8, 1, 1 H), 7.82 (s br, 1 H). Anal. ($C_{17}H_{16}N_2O_3 \cdot 0.3H_2O$) C, H, N.

***trans*-3,4-Dihydro-6-(1*H*-imidazo[4,5-*c*]pyrid-2-yl)-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol (20b).** Aldehyde **20** (R = CHO; 867 mg, 3 mmol), 3,4-diaminopyridine (371 mg, 3.4 mmol), and sodium disulfite (486 mg, 2.6 mmol) were stirred in *N*,*N*-dimethylacetamide (8 mL) for 1.5 h at 130 °C. The solution was then poured into H_2O (50 mL) and the precipitate isolated to yield 600 mg (53%) of **20b**: mp >310 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.25 (s, 3 H), 1.50 (s, 3 H), 2.02 (m, 2 H), 2.50 (m, 2 H), 2.98 (m, 1 H), 3.38 (m, 1 H), 3.78 (m, 1 H), 5.12 (d, 9.5, 1 H), 5.71 (d, 5, 1 H), 7.00 (d, 9, 1 H), 7.55 (s br, 1 H), 7.81 (s, 1 H), 8.09 (d, 8.5, 1 H), 8.3 (d, 5, 1 H), 8.91 (s br, 1 H), 13.26 (s br, 1 H). Anal. ($C_{21}H_{22}N_4O_3 \cdot 0.1H_2O$) C, H, N.

***trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-thioureido-2*H*-1-benzopyran-3-ol (20k).** Benzoyl chloride (3.2 mL, 27.5 mmol) was added dropwise to sodium thiocyanate (2.4 g, 29.6 mmol) in dry acetone (100 mL) and this mixture subsequently heated at reflux for 15 min, during which a crystalline precipitate was formed. Amine **20** (R = NH_2; 6.9 g, 25 mmol), dissolved in a little acetone, was added dropwise to the cooled suspension and then heated at reflux for 2 h. The solution was evaporated, the residue treated with H_2O (500 mL), and the solid material isolated and dried in the air to give 10.2 g (93%) of crude *trans*-6-(3-benzoylthioureido)-3,4-dihydro-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol. **20** (R = PhCONHCSNH; 10.2 g, 23.2 mmol) was stirred in a solution of K_2CO_3 (4.8 g, 35 mmol) in H_2O/MeOH (30 mL/150 mL) for 2.5 h at room temperature. The solution was evaporated to a residue which was treated with H_2O (450 mL) and the water decanted; the solid dried in the air to give 7.5 g (93%) of **20k**: mp 235–237 °C (MeOH); NMR (DMSO-d_6) δ 1.18 (s, 3 H), 1.40 (s, 3 H), 1.97 (m, 2 H), 2.39 (m, 2 H), 2.99 (m, 1 H), 3.30 (m, 1 H), 3.75 (dd, 10, 5, 1 H), 4.98 (d, 10, 1 H), 5.55 (d, 5, 1 H), 6.74 (d, 8.2, 1 H), 6.89 (d, 2, 1 H), 7.09 (dd, 8.2, 2, 1 H), 7.28 (s br, 2 H), 9.45 (s, 1 H). Anal. ($C_{16}H_{21}N_3O_3S$) C, H, N, S.

***trans*-3,4-Dihydro-2,2-dimethyl-6-(4-methyl-2-thiazolylamino)-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol (20l).** Compound **20k** (3.3 g, 9.8 mmol) and chloroacetone (1 mL, 12.4 mmol) were heated at reflux overnight in EtOH (100 mL). The solution was evaporated to a residue which was dissolved in H_2O (50 mL) and made alkaline with 1 N NaOH; the precipitated crystals were isolated and dried in the air to yield 1.8 g (49%) of **20l**: mp 255 °C (EtOH); NMR (DMSO-d_6) δ 1.16 (s, 3 H), 1.40 (s, 3 H), 1.99 (m, 2 H), 2.17 (s, 3 H), 2.39 (m, 2 H), 2.95 (m, 1 H), 3.32 (m, 1 H), 3.64 (d, 9.8, 1 H), 4.96 (d, 9.8, 1 H), 5.51 (s br, 1 H), 6.34 (s, 1 H), 6.73 (d, 8.9, 1 H), 7.27 (d, 1, 1 H), 7.30 (dd, 8.9, 1, 1 H), 9.88 (s br, 1 H). Anal. ($C_{19}H_{23}N_3O_3S$) C, H, N, S.

***trans*-3,4-Dihydro-2,2-dimethyl-6-[(4-nitrobenzylidene)amino]-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol (20g).** Amine **20** (R = NH_2; 550 mg, 2 mmol) and 4-nitrobenzaldehyde (300 mg, 2 mmol) were heated at reflux in EtOH (20 mL) for 2 h. Compound **20g** was filtered off and dried to give 750 mg (92%) of yellow crystals: mp 250–252 °C; NMR (DMSO-d_6) δ 1.18 (s, 3 H), 1.44 (s, 3 H), 1.98 (m, 2 H), 2.40 (m, 2 H), 2.95 (m, 1 H), 3.30 (m, 1 H), 3.69 (dd, 10, 5.5, 1 H), 4.99 (d, 10, 1 H), 5.59 (d, 5.5, 1 H), 6.82 (d, 8.4, 1 H), 6.87 (d, 1.6, 1 H), 7.25 (dd, 8.4, 1.6, 1 H), 8.10 (d, 8.4, 2 H), 8.30 (d, 8.4, 2 H), 8.72 (s, 1 H). Anal. ($C_{22}H_{23}N_3O_5$) C, H, N.

***trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-(5-tetrazolyl)-2*H*-1-benzopyran-3-ol (20m).** Nitrile **20a** (2.9 g, 10.1 mmol), sodium azide (1.34 g, 20.6 mmol), and NH_4Cl (680 mg, 12.7 mmol) were heated at reflux in dry DMF (5 mL) under N_2 for 24 h. After cooling, H_2O (100 mL) was added, and the crystals were separated to yield 2.5 g (75%) of **20m**: mp 296–297 °C; NMR (DMSO-d_6) δ 1.21 (s, 3 H), 1.45 (s, 3 H), 1.97 (m, 2 H), 2.42 (m, 2 H), 2.90 (m, 1 H), 3.30 (m, 1 H), 3.71 (dd, 9.2, 5.2, 1 H), 5.04 (d, 9.2, 1 H), 5.69 (d, 5.2, 1 H), 6.98 (d, 8.4, 1 H), 7.55 (d, 1.2, 1 H), 7.81 (dd, 8.4, 1.2, 1 H), 16.30 (s br, 1 H). Anal. ($C_{16}H_{19}N_5O_3$) C, H, N.

Methyl *trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carboximidate Dihydrochloride (20n). Compound **20a** (20 g, 69.8 mmol) was suspended in MeOH (800 mL). This was saturated with HCl with ice cooling, a clear solution eventually forming. After standing overnight, the solution was evaporated down to a volume of 50 mL and cooled; the precipitated crystals were collected and washed with Me_2CHOH and with Et_2O to yield 22 g (80%) of **20n**: mp 164–166 °C; NMR (DMSO-d_6) δ 1.19 (s, 3 H), 1.45 (s, 3 H), 1.99 (m, 2 H), 2.41 (m, 2 H), 2.89 (m, 1 H), 3.07 (s, 3 H), 3.34 (m, 1 H), 3.69 (d, 10.2, 1 H), 5.00 (d, 10.2, 1 H), 6.80 (d, 7.8, 1 H), 7.44 (d, 1.4, 1 H), 7.72 (dd, 7.8, 1.4, 1 H), 8.30 (s br). Anal. ($C_{17}H_{22}N_2O_4 \cdot 2HCl$) C, H, Cl, N.

***trans*-3,4-Dihydro-6-(2-imidazolin-2-yl)-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol (20o).** Imino ether **20n** (1.7 g, 4.3 mmol) and ethylenediamine (1.2 g, 20 mmol) were added to MeOH (20 mL), the temperature rising slightly, and the mixture was left to stand at room temperature for 2 h. The solution was evaporated to a residue which was crystallized from H_2O to give 1.6 g (98%) of **20o**: mp 202–206 °C (Me_2CHOH); NMR (DMSO-d_6) δ 1.18 (s, 3 H), 1.45 (s, 3 H), 1.95 (m, 2 H), 2.39 (m, 2 H), 2.89 (m, 1 H), 3.30 (m, 1 H), 3.60 (s, 4 H), 3.69 (d, 10.6, 1 H), 5.00 (d, 10.6, 1 H), 5.69 (s br), 6.82 (d, 8.5, 1 H), 7.37 (d, 1, 1 H), 7.65 (dd, 8.5, 1, 1 H). Anal. $C_{18}H_{23}N_3O_3$) C, H, N.

***trans*-3-(Formyloxy)-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (21a).** Formic acid (11.7 mL, 310 mmol) and Ac_2O (3.3 mL, 35 mmol) were mixed with ice cooling, after which **7e** (2 g, 6.7 mmol) was added and the reaction mixture heated to 42 °C for 3 h. The solution was evaporated and the residue chromatographed on a silica gel column (CH_2Cl_2/EtOAc 1:1) to yield 1.08 g (49%) of **21a**: mp 203.5–204 °C; NMR (DMSO-d_6, 390 K) δ 1.36 (s, 3 H), 1.45 (s, 3 H), 5.72 (d, 9.6, 1 H), 5.92 (d br, 9.5, 1 H), 6.19 (td, 6.8, 1.5, 1 H), 6.37 (dt, 9.17, 2.2, 1 H), 7.02 (d, 8.6, 1 H), 7.06 (d, 2, 1 H), 7.37 (td, 9.2, 6.5, 2, 1 H), 7.45 (dd, 6.9, 2, 1 H), 7.57 (dd, 8.5, 2.1, 1 H), 8.14 (s, 1 H). Anal. ($C_{18}H_{16}N_2O_4 \cdot 0.1H_2O$) C, H, N.

***trans*-3,4-Epoxy-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (22a).** Chromene **18a** (12.4 g, 44.6 mmol) was dissolved in CH_2Cl_2 (93 mL); a solution of 3-chloroperbenzoic acid (13.6 g, 79 mmol) in CH_2Cl_2 (155 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 days and the precipitate removed. The mother liquor was extracted with dilute NaOH, and the organic phase dried. The solvent was evaporated and the residue chromatographed through a silica gel column. The chromatographically homogeneous fractions were combined to yield 7.1 g (54%) of **22a**: mp 128–131 °C ($(Me_2CH)_2O$/Et_2O 1:1); NMR ($CDCl_3$) δ 1.50 (s, 3 H), 1.55 (s, 3 H), 3.69 (s, 1 H), 6.35 (td, 6.7, 1, 1 H), 6.58 (dd, 8.8, 1, 1 H), 6.94 (d, 8.1, 1, H), 7.06 (d, 2.1, 1 H), 7.42–7.57 (m, 3 H). Anal. ($C_{17}H_{14}N_2O_3 \cdot 0.1H_2O$) C, H, N.

3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-3-oxo-2*H*-1-benzopyran-6-carbonitrile (23a). HCl gas was passed into a boiling solution of epoxide **22a** (17 g, 57.8 mmol) in absolute dioxane (150 mL) for 45 min. After cooling, the solution was diluted with Et_2O (100 mL), **23a** precipitating as crystals: yield 15 g (88%); mp 175–178 °C (Me_2CHOH); NMR data of the keto species ($CDCl_3$) δ 1.54 (s, 3 H), 1.61 (s, 3 H), 6.10 (s br, 1 H), 6.35 (td, 6.7, 0.7, 1 H), 6.65 (d, 8.8, 1 H), 7.02–7.18 (m, 3 H), 7.49 (td, 7.7, 1.4, 1 H), 7.58 (dd, 8.1, 1, 1 H). Anal. ($C_{17}H_{14}N_2O_3 \cdot 0.1H_2O$) C, H, N.

3,4-Dihydro-2,2-dimethyl-4-oxo-3-(2-pyridyloxy)-2*H*-1-benzopyran-6-carbonitrile (24). Epoxide **22a** (500 mg, 1.7 mmol), liquid NH_3 (1 mL), and EtOH (10 mL) were heated at 130 °C in a bomb tube for 15 min. The tube was then opened and heated for another 15 min at 130 °C to evaporate the volatile components. The residue was recrystallized from a small quantity of $(Me_2CH)_2O$ to give 300 mg (60%) of **24**: mp 110–112 °C; NMR ($CDCl_3$ + D_2O) δ 1.48 (s, 3 H), 1.62 (s, 3 H), 6.23 (s, 1 H), 6.84–7.0

(m, 2 H), 7.08 (d, 8.1, 1 H), 7.49–7.79 (m, 2 H), 8.09 (dd, 5.3, 1.4, 1 H), 8.15 (d, 2.1, 1 H). Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

***cis*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (7ab).** Ketone **23a** (3 g, 10.1 mmol) was dissolved in MeOH (50 mL) and $NaBH_4$ (750 mg, 19.8 mmol) was added in portions. After 1 h the solvent was evaporated off; the residue was dissolved in H_2O (100 mL) and the solution extracted with CH_2Cl_2 (200 mL). The organic phase was dried and evaporated to a residue in a Rotavapor; the residue was recrystallized from a little MeOH: yield 2.1 g (70%) **7e**, mp 245–246 °C. The mother liquor was chromatographed through a LiChrosorb Si 60 steel column (E. Merck, Cat. No. 9387; CH_2Cl_2/MeOH 95:5), and the homogeneous fractions of **7ab** were combined: yield 130 mg (4.3%); mp 210–212 °C (Et_2O); NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.56 (s, 3 H), 2.87 (d br, 5.6, 1 H), 3.95 (dd, 5.6, 3.5, 1 H), 6.17 (t, 6.3, 1 H), 6.59 (m, 2 H), 7.00 (d, 7.8, 1 H), 7.13 (s **br**, 1 H), 7.19 (dd, 7, 0.7, 1 H), 7.39 (ddd, 8.8, 6.7, 1.7, 1 H), 7.50 (dd, 8.8, 1.7, 1 H). Anal. ($C_{17}H_{16}N_2O_3 \cdot 0.1H_2O$) C, H, N.

4-(1,2-Dihydro-2-oxo-1-pyridyl)-3-methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (25c). Ketone **23a** (600 mg, 2 mmol), dimethyl sulfate (0.2 mL, 2.1 mmol), K_2CO_3 (600 mg, 4.3 mmol), and Me_2CO (20 mL) were stirred overnight at room temperature. The precipitate was removed and the mother liquor evaporated. The residue was mixed with a little Et_2O and crystallized to yield 400 mg (60%) of **25c**: mp 186–188 °C; NMR ($CDCl_3$) δ 1.54 (s, 3 H), 1.59 (s, 3 H), 3.63 (s, 3 H), 6.34 (td, 7.1, 0.9, 1 H), 6.71 (d, 9.1, 1 H), 6.76 (d, 1.1, 1 H), 6.87 (d, 7.6, 1 H), 7.16 (dd, 7.1, 1.4, 1 H), 7.35 (dd, 8.1, 1.7, 1 H), 7.51 (ddd, 8.8, 6.7, 1.7, 1 H). Anal. ($C_{18}H_{16}N_2O_3 \cdot 0.2H_2O$) C, H, N.

***trans*-3,4-Dibromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (26).** Br_2 (1.8 mL, 35.1 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise to a solution of chromene **4e** (6.7 g, 36.2 mmol) in CH_2Cl_2 (20 mL) at 10 °C within 15 min. The solvent was evaporated and the residue crystallized from Et_2O to yield 9.1 g (73%) of **26**: mp 111–113 °C; NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.69 (s, 3 H), 4.45 (d, 7.2, 1 H), 5.48 (d, 7.2, 1 H), 6.88 (d, 7.9, 1 H), 7.47 (dd, 7.9, 1.4, 1 H), 7.83 (d, 1.4, 1 H). Anal. ($C_{12}H_{11}Br_2NO \cdot 0.1H_2O$) C, H, Br, N.

4-Chloro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (27). Chromanone **2e** (2.8 g, 13.9 mmol) and PCl_5 (3.1 g, 14.9 mmol) were heated at reflux in a mixture of absolute benzene (25 mL) and CS_2 (5 mL) for 20 h. The solvents were evaporated, and the residue was chromatographed on a silica gel column (CH_2Cl_2). The nonpolar main product was crystallized from *n*-hexane to yield 900 mg (29%) of **27**: mp 38–40 °C; NMR ($CDCl_3$) δ 1.50 (s, 6 H), 5.84 (s, 1 H), 6.84 (d, 7.7, 1 H), 7.47 (dd, 7.7, 1.2, 1 H), 7.70 (d, 1.2, 1 H). Anal. ($C_{12}H_{10}ClNO \cdot 0.1H_2O$) C, H, Cl, N.

3-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (28). Dibromide **26** (10.5 g, 30.2 mmol), 2-pyridone (8.7 g, 91.5 mmol), and K_2CO_3 (12.3 g, 89 mmol) in DMF (150 mL) were heated at 130 °C for 1 h. After cooling, the precipitate was filtered off and discarded. The mother liquor was mixed with H_2O (500 mL) and extracted with EtOAc. The organic phase was evaporated to a residue which was chromatographed on a silica gel column ($Et_2O \rightarrow$ EtOAc) to give 1.46 g (17%) of **28**: mp 116–118 °C; NMR ($CDCl_3$) δ 1.55 (s, 6 H), 6.20 (td, 6.7, 1 H), 6.49 (s, 1 H), 6.58 (d, 9.9, 1 H), 6.97 (d, 7.7, 1 H), 7.18 (dd, 6.7, 1.4, 1 H), 7.33–7.46 (m, 2 H), 7.50 (dd, 7.7, 1.4, 1 H). Anal. ($C_{17}H_{14}N_2O_2 \cdot 0.7H_2O$) C, H, N.

Antihypertensive Studies in Conscious Spontaneously Hypertensive Rats. Compounds were tested for antihypertensive action in conscious spontaneously hypertensive male rats (280–330 g; blood pressure > 180 mmHg; origin: Okamoto-strain). Arterial pressure was recorded directly via an aortic catheter to determine the potency of substance (mean arterial blood pressure) in unrestrained animals and indirectly (to evaluate the duration of action of the substance) by means of a plethysmographic method (measurement of the systolic blood pressure) in restrained animals.

For direct recording of arterial blood pressure an HSE setup (Statham pressure transducer, Watanabe recorder, HSE oscilloscope) was used while IITC equipment (tail cuff, photoelectric sensor) was used for the indirect measurement. With the direct method, the blood pressure was recorded continuously over a period from 1 h before to 3.5 h after administration of the substance; to assess the effects of the substance, the mean of the maximum individual changes in the 3.5-h period after administration was used. With the indirect method, measurements were made prior to and 2 and 20 h postadministration of the compound. For each compound 1 mg/kg was administered orally as a screening dose; two to four additional doses of the compounds that proved active at 1 mg/kg in reducing blood pressure were tested, and an ED_{30} (= dose in μg/kg that reduces blood pressure by 30 mmHg) was calculated from a linear regression of effect vs log dose. The substances were suspended in 5% gum arabic and administered orally by gavage.

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Registry No. 1, 35794-84-4; **2c**, 121021-84-9; **2e**, 121021-88-3; **3c**, 123595-58-4; **3e**, 123595-59-5; **4c**, 123595-60-8; **4e**, 33143-29-2; **5a**, 123595-62-0; **5b**, 123595-63-1; **5c**, 123595-61-9; **5d**, 123595-64-2; **5e**, 75611-72-2; **5** (R_1 = Me; R_2 = COMe), 123595-65-3; **5** (R_1 = Me; R_2 = NO_2), 68196-67-8; **5** (R_1 = Me; R_2 = COOEt), 123595-66-4; **5** (R_1 = Me; R_2 = COOMe), 123595-67-5; **5** (R_1 = Me; R_2 = 4-pyridyl), 123595-68-6; **5** (R_1 = Me; R_2 = Br), 123595-69-7; **6** (R_3 = R_4 = R_5 = H), 142-08-5; **6** (R_3 = R_5 = Br; R_4 = H), 13472-81-6; **6** (R_3 = R_4 = H; R_5 = NO_2), 5418-51-9; **6** (R_3 = NO_2; R_4 = R_5 = H), 6332-56-5; **6** (R_3 = R_5 = Cl; R_4 = H), 5437-33-2; **6** (R_3 = R_4 = H; R_5 = Cl), 4214-79-3; **6** (R_3 = R_4 = H; R_5 = CO_2H), 5006-66-6; **6** (R_3 = CO_2H; R_4 = R_5 = H), 609-71-2; **6** (R_3 = R_4 = H; R_5 = NHCOMe), 41292-43-7; **6** (R_3 = NHCOMe; R_4 = R_5 = H), 76349-07-0; **6** (R_3 = OCOMe; R_4 = R_5 = H), 61296-14-8; **6** (R_3 = OMe; R_4 = R_5 = H), 20928-63-6; **6** (R_3 = R_5 = H; R_4 = OBzl), 53937-02-3; **6** (R_3 = R_5 = H; R_4 = OMe), 52545-13-8; **6** (R_3 = R_5 = H; R_4 = OEt), 7020-68-0; **6** (R_3 = $N(CH_3)_2$; R_4 = R_5 = H), 33252-49-2; **7a**, 123595-80-2; **7b**, 123595-81-3; **7c**, 123595-82-4; **7d**, 123595-83-5; **7e**, 123595-75-5; **7f**, 123595-84-6; **7g**, 123595-85-7; **7h**, 123595-78-8; **7i**, 123595-76-6; **7j**, 123595-77-7; **7k**, 123595-86-8; **7l**, 123595-87-9; **7m**, 123595-88-0; **7n**, 123595-89-1; **7o**, 123595-90-4; **7p**, 123595-91-5; **7q**, 123595-92-6; **7r**, 123595-93-7; **7s**, 123595-94-8; **7t**, 123595-95-9; **7u**, 123595-96-0; **7v**, 123595-97-1; **7w**, 123595-98-2; **7x**, 123595-99-3; **7y**, 123595-00-9; **7z**, 123595-01-0; **7aa**, 123596-02-1; **7ab**, 123596-03-2; **7ac**, 123595-79-9; **7ad**, 123596-04-3; **7ae**, 123596-05-4; **7af**, 123596-06-5; **7ag**, 123596-07-6; **8**, 123596-08-7; **9a**, 123596-09-8; **9b**, 123596-10-1; **9c**, 123596-11-2; **9d**, 123596-12-3; **9e**, 123596-13-4; **9f**, 123596-14-5; **9g**, 123596-15-6; **9h**, 123596-16-7; **9i**, 123596-17-8; **9j**, 123596-18-9; **9k**, 123596-19-0; **9l**, 123596-20-3; **9m**, 123596-21-4; **9n**, 123596-22-5; **10**, 123596-23-6; **11**, 123596-24-7; **12**, 123596-25-8; **13** (R_1 = CN), 123595-70-0; **13** (R_1 = NO_2), 123595-71-1; **15a**, 123596-26-9; **15b**, 123596-27-0; **15c**, 123596-68-9; **15c**·HCl, 123596-28-1; **15d**, 123596-29-2; **15e**, 123596-69-0; **15e**·HCl, 123596-30-5; **16**, 123595-72-2; **17a**, 123596-31-6; **17b**, 123596-32-7; **18a**, 117545-11-6; **18b**, 117545-39-8; **18c**, 117545-37-6; **18d**, 117545-13-8; **18e**, 117545-25-2; **18f**, 117545-28-5; **18g**, 117545-31-0; **18h**, 117545-35-4; **18i**, 117545-18-3; **18j**, 117545-41-2; **18k**, 117545-64-9; **18l**, 123596-33-8; **18m**, 117545-66-1; **18n**, 117545-55-8; **18o**, 117545-56-9; **18p**, 117545-34-9; **18q**, 117545-35-0; **18r**, 117545-36-1; **18s**, 117545-37-2; **18t**, 117545-38-3; **18u**, 117545-65-0; **18v**, 122262-12-8; **19a**, 123596-39-4; **19b**, 123596-40-7; **19c**, 117545-46-7; **19d**, 117545-51-4; **19e**, 123596-41-8; **19f**, 117545-16-1; **19g**, 123596-42-9; **20a**, 94470-67-4; **20b**, 123596-43-0; **20c**, 123596-44-1; **20d**, 123596-45-2; **20e**, 123596-46-3; **20f**, 123596-58-7; **20f**·HCl, 123596-47-4; **20g**, 123596-48-5; **20h**, 123596-49-6; **20i**, 123596-50-9; **20j**, 123596-51-0; **20k**, 123596-52-1; **20l**, 123596-53-2; **20m**, 123596-54-3; **20n**, 123596-59-8; **20n**·2HCl, 123596-55-4; **20o**, 123596-56-5; **20p**, 123596-57-6; **20** (R = CHO), 103732-25-8; **20** (R = NH_2), 123595-73-3; **20** (R = PhCONHCSNH), 123595-74-4; **20** (R = $CONH_2$), 123596-76-9; **21a**, 123596-60-1; **21b**, 123596-61-2; **21c**, 123596-62-3; **22a**, 123596-63-4; **22b**, 123596-64-5; **22c**, 123596-65-6; **23a**, 123596-66-7; **23b**, 123596-67-8; **24**, 123596-70-3; **25b**, 123596-71-4; **25c**, 123596-72-5; **26**, 123596-73-6; **27**, 123596-74-7; **28**, 123596-75-8; MeCOMe, 67-64-1; PhOH, 108-95-2; $Cl(CH_2)_3CN$, 628-20-6; $Cl(CH_2)_4CN$, 6280-87-1; *p*-$NO_2C_6H_4CHO$, 555-16-8; *p*-CNC_6H_4CHO, 105-07-7; $(EtO)_2P(O)CH_2CN$, 2537-48-6;

p-$(EtO)_2P(O)CH_2C_6H_4CN$, 1552-41-6; o-$H_2NC_6H_4NH_2$, 95-54-5; cyclohexanone, 108-94-1; 3,5-dichloro-4-hydroxypyridine, 17228-71-6; 4-piperidone hydrochloride, 41979-39-9; 1-hydroxyisoquinoline, 491-30-5; 1,2,3,4-tetrahydro-2,4-dioxopyrimidine, 66-22-8; 4-hydroxypyridine, 626-64-2; 3-hydroxypyridazine, 504-30-3; 1,4,5,6-tetrahydropyridazin-6-one, 61468-81-3; pyrimidin-4-ol, 4562-27-0; 6-hydroxy-3-pyridazinecarboxylic acid ethyl ester, 63001-31-0; 1,1-dioxo-3,4,5,6-tetrahydro-1,2-thiazine, 37441-50-2; 2-hydroxypyrazine, 6270-63-9; pyrimidin-2-ol hydrochloride, 38353-09-2; 1-hydroxy-2,3-benzodiazine, 119-39-1; 3-hydroxypyridine, 109-00-2; 4-pyridinecarbonyl chloride, 14254-57-0; chloroacetone, 78-95-5; 2,4-dichlorobenzaldehyde, 874-42-0; ethylenediamine, 107-15-3; 3,4-diaminopyridine, 54-96-6; 2,3-diaminopyridine, 452-58-4; 2-pyrrolidinone, 616-45-5.

Synthesis and Antiinflammatory Activity of *cis*- and *trans*-6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic and -oxepinacetic Acids

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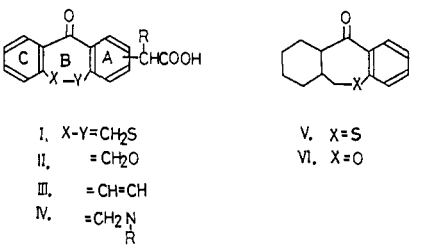
A series of *cis*- and *trans*-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids (**6–9**) and -oxepinacetic acids (**10–13**) were prepared and their antiinflammatory activity was examined in the rat carrageenan hind paw edema test. The antiinflammatory activity of these compounds depended on their stereochemical feature (C6a, C10a, and C2'). The 6a,10a-trans compounds exhibited considerable antiinflammatory activity, whereas the 6a,10a-cis compounds were inactive. Among the trans compounds, 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin-3-propionic acid (**9a**) and its oxepin analogue (**13a**) showed an antiinflammatory activity superior to that of indomethacin. The phenethyl ester (**25**) of **9a** showed potent antiinflammatory activity, and its safety index (UD_{50}/ED_{50}) was over 14 times higher than that of indomethacin. The phenethyl ester (**25**) is the most favorable compound with high antiinflammatory activity and little ulcerogenicity.

Vane et al.[1] found that nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin and indomethacin had an inhibitory activity on prostaglandin biosynthesis and this activity was correlative with their antiinflammatory activity. Shen[2] has proposed an interesting hypothesis concerning the receptor-site model for NSAIDs.

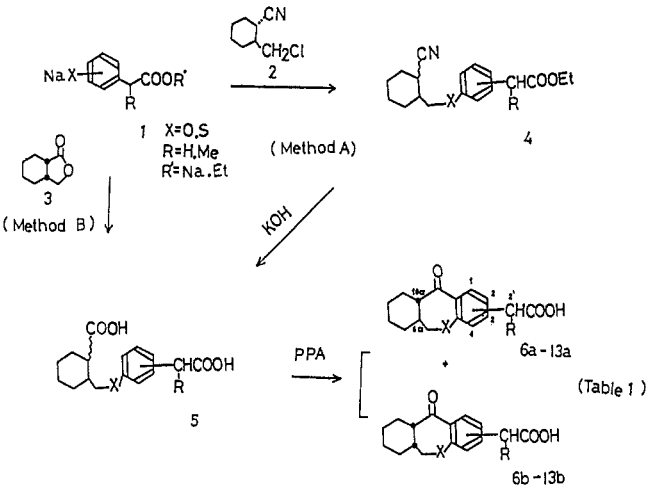
Many tricyclic arylacetic acids having a 6–7–6-membered ring have recently been reported as potent antiinflammatory agents, for example, dibenzothiepin- (I),[3] dibenzoxepin- (II),[4] dibenzotroponone- (III),[5] and dibenzazepinacetic acids (IV).[6] In each of these, two six-membered rings consist of benzene rings.

Since it is of interest for us to examine the effect of partial saturation of the 6–7–6-ring system on the antiinflammatory properties of this class of NSAIDs, we had studied 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin (V) and -oxepin (VI) derivatives[7] (Chart I). As an extension of these works, we now wish to report the synthesis and preliminary pharmacological evaluation of a number of octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids (**6–9**) and their oxepin analogues (**10–13**). Some of them were highly active in animal models as NSAIDs. On the basis of these data, compound **9a** appears to offer several advantages over indomethacin.

Chart I



Scheme I



In the clinical use of NSAIDs, gastrointestinal lesions have been the most troublesome problem. In order to lessen this side effect, **9a** was led to its esters and amides. Among the synthesized compounds, the phenethyl ester (**25**) of **9a** showed a potent antiinflammatory activity and weak irritative effect on gastric mucosa, and hence was selected for further investigation.

Chemistry. The *cis*- and *trans*-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepinacetic acids (**6–9**) and -oxepinacetic acids (**10–13**) were synthesized by the two

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