The Influence of Substituents in 3-Position on the Activity of Chroman-Type Potassium Channel Activators

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Received March 17, 1993

Swern oxidation of chromanol **1** led to ketone **3** with concomitant chlorination of the adjacent 4-position. Using *Leuckart* conditions, chromanone **2** was converted to enamine **5**. - 4-Bromochromene-3-carbaldehyde **8**, which was obtained by *Vilsmeier-Arnold* reaction from **7**, turned out to be a suitable intermediate for the insertion of the pyridone residue. 3-Chloro derivatives **16** and **19** resulted on heating the mesylate or tosylate with LiCl in DMF. Bromination of chromene **20** led to **21**. - All compounds were tested for oral antihypertensive activity in spontaneously hypertensive rats with a dose of 1 mg/kg.

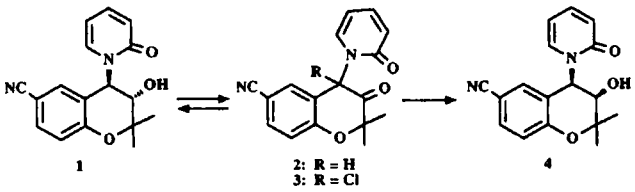
Der Einfluß von Substituenten in der 3-Stellung auf die Wirkstärke von Kaliumkanalaktivatoren vom Chromantyp

Swern-Oxidation von Chromanol **1** führte unter gleichzeitiger Chlorierung der benachbarten 4-Stellung zum Keton **3**. Unter Bedingungen der *Leuckart*-Reaktion wurde das Chromanon **2** in das Enamin **5** übergeführt. Als geeignetes Zwischenprodukt für die Einführung des Pyridonrests erwies sich der 4-Bromchromen-3-carbaldehyd **8**, der durch *Vilsmeier-Arnold* Reaktion aus **7** erhalten wurde. Die 3-Chlorderivate **16** und **19** resultierten aus dem Mesylat bzw. Tosylat durch Erhitzen mit LiCl in DMF. Die Bromierung des Chromens **20** führte zu **21**. - Die blutdrucksenkende Aktivität der Verbindungen wurde an spontan hypertensiven Ratten nach oraler Gabe mit einer Dosierung von 1 mg/kg getestet.

Potassium channel openers which relax smooth muscles by activating potassium channels have attracted increasing attention, since they have a high potential in the treatment of diseases[1] caused by smooth muscle contraction such as hypertension, angina pectoris, bronchial asthma, and urinary incontinence. In particular the 2*H*-1-benzopyrans have proved to be of great interest within the different structural classes of K^+ channel activators. Since their discovery the lead compound cromakalim has been modified in many ways[2]. Replacement of the 4-(2-oxo-1-pyrrolidinyl) group with an α-pyridone (**1**, emakalim) and with heterocyclyloxy groups (*e.g.* **17**, EMD 57 283) as well as the unsaturated chromene structure (bimakalim) represented some early alterations displaying higher potency in preclinical studies.

Relatively little is known about the influence of substituents in the 3-position on activity. *Buckle et al.*[3] replaced the hydroxyl group of cromakalim by methyl carboxylate, carboxylic, keto, hydroxymethyl, aldehyde, methoxymethyl, fluoromethyl, and nitro groups. With the exception of the 3-keto analogue of cromakalim, none of these compounds showed marked spasmolytic activity. The 3-methyl-4-heterocyclyloxy chromanols[4] belong to the most potent potassium channel activators known to date. However, the nature of the 3-methyl group is contradictory, since there are examples where this group leads to considerable loss of potency. In the following we report on further structural modifications of the C-3 position of 2*H*-1-benzopyrans and their effects on antihypertensive activity.

Ketone **2** represents an attractive intermediate for the introduction of further substituents in C-3. **2** could not be obtained by direct oxidation of the readily available alcohol **1**. It was prepared by acid-catalyzed rearrangement of the 3,4-epoxy compound[5]. The synthesis of the appropriate 3-keto analogue of cromakalim was considerably less straightforward[3].



Scheme 1

On oxidation of alcohol **1** using *Swern* conditions[6] (DMSO/oxalyl chloride), we were surprised to find that a chlorine atom was simultaneously introduced in the C-4 position to give **3** (Scheme 1; only relative stereochemistry is shown). Similar one-step oxidation/halogenation reactions were observed in the treatment of 3-hydroxysteroids with *tert*-butyl hypochlorite, *N*-bromosuccinimide, *N*-chlorosuccinimide, and *N*-bromoacetamide[7]. Although compound **3** shows strong carbonyl absorption at 1738 cm^{-1}, final structural assignment was obtained from X-ray analysis (Fig. 1).

The benzylic proton of compound **2** in position 4 is further activated by the keto group and the pyridone ring. The ketone is to some extent in equilibrium with its enol form. It is likely that the proton was replaced by excessive chlorodimethylsulfonium intermediate by electrophilic attack. Mild reduction conditions like $NaBH_4$ in MeOH resulted in the loss of the chlorine atom and the appearance of a mixture of the diastereomeric alcohols **1** and **4**[5]. In accordance with others[3] we found cromakalim not to be oxidizable using *Swern* conditions.

Keto compound **2** should be a suitable starting material for the synthesis of the so far unknown 3-amino-4-heterocyclyl substituted 2*H*-1-benzopyrans. According to a

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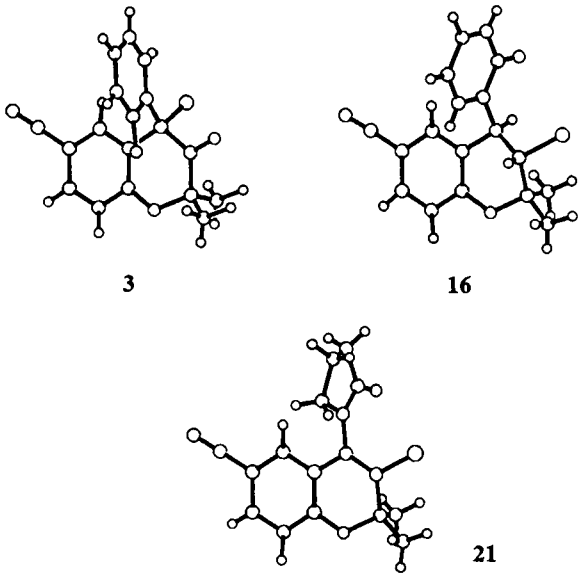
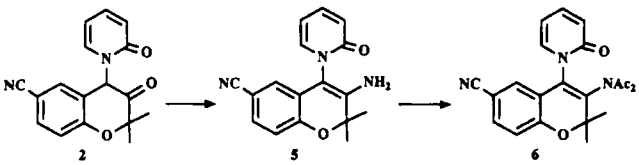
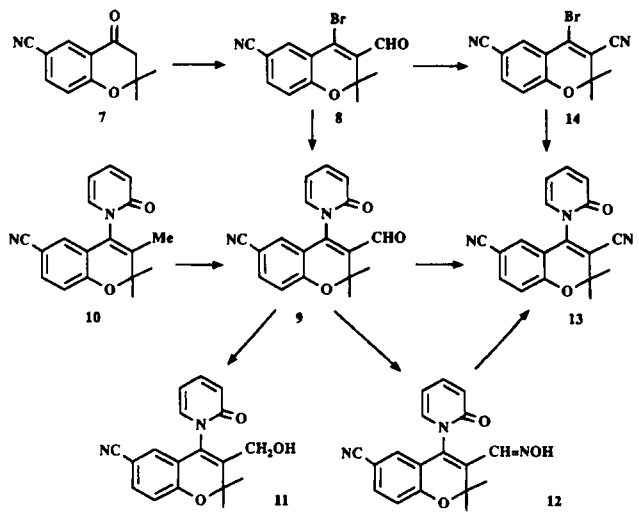


Figure 1: X-ray crystal structures of compounds **3**, **16**, and **21**.



Scheme 2



Scheme 3

new variant of the *Leuckart* reaction[8], **2** was reacted in a sealed tube with formamide in the presence of a catalytic amount aluminum chloride at 170°C (Scheme 2). The reaction resulted not in the expected 3-formylamino chromane derivative but afforded enamine **5** in high yield. Obviously, the reduction step of the *Leuckart* reaction was prevented here due to high steric hindrance. This observation is in contrast to the results of *Agwada* and *Awachie*[9]. They stated that reduction is the primary step of the reaction. A two-proton signal in its ^{1}H-NMR-spectrum is indicative of the product **5** in its enamine form. Acetylation of **5** required forcing conditions and led to diacetate **6**.

Using the *Vilsmeier-Arnold* reaction[10] with DMF/PBr_3 the ketone **7** was converted into 4-bromo-3-formyl-chromene **8** in moderate yield (Scheme 3). On heating **8** with 2-pyridinol in DMF/K_2CO_3 the pyridone residue was inserted, presumedly by an addition/elimination process (→ **9**). Aldehyde **9** could also be isolated in poor yield on treatment of **10** with methyl lithium[4] and subsequent oxidative workup. $NaBH_4$-reduction of **9** led to alcohol **11**. Aldehyde **9** was converted directly into the nitrile **13** when treated with hydroxylamine hydrochloride/formic acid under reflux. At room temp. the intermediate oxime **12** could be isolated. Alternatively **13** was formed by treatment of **14** with pyridone.

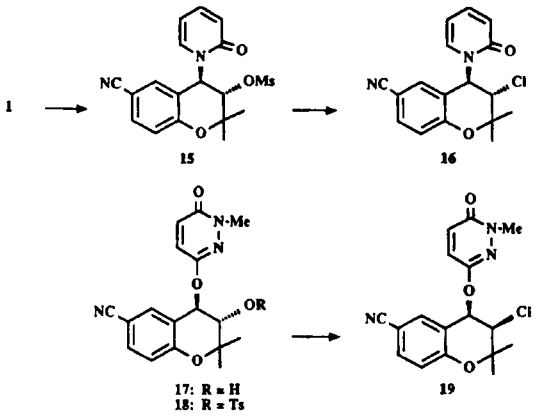
Only one K^+ channel activator bearing a halogen atom at C-3 has been described[11]. It was isolated in trace amounts on treatment of the corresponding alcohol with diethylaminosulphur trifluoride (DAST). We obtained a 4% yield of chloro derivative **16** on heating the mesylate **15** with LiCl in DMF[12] (Scheme 4; only relative stereochemistry is shown). Substitution took place with retention of *trans* configuration, which was verified by X-ray diffraction (Figure 1). In analogy to the paper cited, this unusual finding can be explained by intramolecular displacement of the leaving group at C-3 by the neighbouring pyridone carbonyl group. Following substitution with chloride anion should then lead to the observed product with overall retention.

Employing the same conditions as before the *trans*-alcohol **17** was converted *via* tosylate **18** to chloride **19** with *cis*-configuration. This result supports the hypothesis of a double inversion in the formation of **16**, as the pyridazinone carbonyl should not be capable to displace the leaving group. The *cis* configuration in **19** follows from a small 4.2-Hz coupling constant of 3-H and 4-H, which contrasts to the 11.2-Hz *trans* coupling in **16**. The NMR-spectrum of chloro compound **16** shows a double set of signals similar to the corresponding alcohol **1**[5,13] when recorded in DMSO or $CDCl_3$ at room temp. In both conformational isomers, which are present in a ratio of about 2:1, the *trans* configuration is proved by a complete interpretation of the spectrum.

For bromination of the chromene double bond we chose the 5-ring saturated 4-(2-oxo-1-pyrrolidinyl) compound **20**[14] (Scheme 5). As the 6-cyano group deactivates the benzene nucleus, reaction exclusively occurred at the Δ^3-double bond. We obtained 3-bromo compound **21** by an addition/elimination mechanism in good yield. The structure of **21** was verified by X-ray analysis (Figure 1).

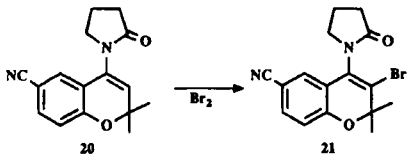
Results and Discussion

The antihypertensive effect of all new compounds was determined after oral administration to conscious spontaneously hypertensive rats (SHR). A direct technique for recording blood pressure (BP) was used. The new com-



Schema 4

pounds and their antihypertensive activities are listed in Table 1 in comparison to two drugs under development by E. Merck: emakalim (**1**) and EMD 57 283 (**17**). Evaluating the compounds it has to be taken into account that standard compounds **1** and **17** represent pure enantiomers whereas



Scheme 5

the new substances **3**, **16**, and **19** are racemates. - The ketone **3** is inactive and the halogen-free analogue **2** shows only weak activity[5]. This might be due to enolisation which gives rise to a certain amount of chromene. The enamine **5** exists fully in the chromene form. Its blood pressure lowering effect is relatively weak, yet slightly higher than that of **2** (38 vs 20 mm Hg). The sterically crowded diacetate **6** is inactive. Scheme 3 contains further chromene structures possessing various residues at C-3. The highest potencies of the series were found in hydroxymethyl compound **11** and aldehyde **9**. Oxime **12** and nitrile **13** were less active. Methyl compound **10**[4] and intermediate **8** do not possess any antihypertensive activity. For compound **8** it can be explained by the missing pyridone residue. Bromo compound **21** also is completely inactive, while for its unbrominated counterpart **20**[14] good activity is reported. The 3-chloro *trans*-chromane **16** is considerably more potent than the *cis* compound **19**. Comparing the new compounds with their highly active 3-hydroxy precursors **1** and **17** it can be concluded that the chlorine substituent cannot compete with the hydroxy group. The poor activity of the *cis*-configuration is in good agreement with earlier observations[5,14].

Table 1: Antihypertensive Effects in Conscious SHR

compound	max fall[a] in BP in mmHg ± SEM
1 (emakalim)	151 ± 9
3	NS[b]
5	38 ± 6
6	NS
8	NS
9	53 ± 10
11	57 ± 9
12	28 ± 9
13	18 ± 7
16	54 ± 4
17 (EMD 57 283)	151 ± 8
19	25 ± 8
21	NS

[a] Mean arterial blood pressure (N ≥ 3) was measured directly before and up to 210 min after oral administration of 1 mg/kg of the test substance.

[b] Compounds that did not lower the blood pressure significantly (< 18 mm Hg).

Prior attempts[3,4] to modify the C-3 hydroxy group of chromanol type K^+ channel activators by introduction of other residues always led to substantial reduction of activity. This applies to the replacement of the chromene 3-H as well. Due to the causal relationship it was unimportant for the structure/activity studies whether the antihypertensive or the relaxing effects were considered. Recently we have reported[4] on the relationship between activity and the angle formed between the nitrogen heterocycle and the benzopyran ring in the crystalline state. An orthogonal orientation of the ring systems to each other seems to be of prime importance for high pharmacological activity. X-ray structural analyses are only available for compounds **3**, **16**, and **21** (Figure 1). In these cases a favorable orthogonal arrangement was found, but only **16** showed appreciable activity. The representation chosen for **3** shows the pyridone carbonyl group pointing forward. This is unusual for this class of compounds. Obviously the space demanding chlorine atom gives rise to the 180° torsion of the pyridone ring.

We extend our thanks to Drs. *Hanns Wurziger* and *Günter Hölzemann* for helpful discussions. We also thank Prof. *Wolfgang Hiller*, TU München, for providing us with X-ray data, Dr. *Michael Krug* for representations of the crystal structures, and Dr. *Volker Eiermann* for the measurement and interpretation of NMR spectra. For their skilful experimental work we would like to thank *Iris Hollerbach*, *Günther Kritzinger*, *Heinrich Kübler*, *Gabriele Pöschl*, *Horst Schiefer*, *Sylvia Wild*, and *Markus Woißyk*.

Experimental Part

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

4-Chloro-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-3-oxo-2H-1-benzopyran-6-carbonitrile (**3**)

A 100-ml three-necked flask equipped with a magnetic stirrer, dropping funnel, drying tube, and thermometer was charged with CH_2Cl_2 (25 ml)

and oxalyl chloride (1 ml, 11.7 mmol). After cooling to -60°C a mixture of DMSO (1.7 ml, 23.9 mmol) and CH_2Cl_2 (5 ml) was added dropwise. Then compound **1**[5] (1.96 g, 6.6 mmol) dissolved in CH_2Cl_2 (20 ml) and DMSO (4 ml, 56 mmol) was added. After 15 min Et_3N (7 ml) was injected and stirring was continued for 5 min at -50°C and for a further 1 h, while the solution was allowed to warm to room temp. The mixture was then poured into H_2O (100 ml), washed with H_2O (100 ml), and the org. phase was evaporated, dried, and chromatographed on a pre-packed silica gel column (LiChroprep Si 60, 40-63 µm, size C; E. Merck) with CH_2Cl_2/EtOAc mixtures using a gradient elution technique: 0.6 g (28%), m.p. 148-149°C (diisopropyl ether).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.60 (s, 3H), 1.61 (s, 3H), 6.45 (d, J = 9.0 Hz, 1H), 6.65 (td, J = 9.0, 9.0, 1.8 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.69 (td, J = 9.0, 8.8, 1.5 Hz, 1H), 7.75 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 8.7, 1.6 Hz, 1H), 8.57 (dd, J = 8.5, 1.7 Hz, 1H).- IR (KBr): 2229 (C≡N), 1738 (C=O), 1657 (C=O) cm^{-1}.- $C_{17}H_{13}ClN_2O_3$ (328.8) Calcd. C 62.1 H 3.99 Cl 10.8 N 8.5 Found C 62.0 H 4.27 Cl 10.6 N 8.4.

Reduction of ketone **3** *to alcohols* **1** *and* **4**

Ketone **3** (0.5 g, 1.5 mmol) was dissolved in MeOH (50 ml) and $NaBH_4$ (0.5 g, 13.2 mmol) was added in portions at 5°C with stirring. After 1.5 h the solvent was evaporated. The residue was dissolved in H_2O (20 ml) and the solution extracted with EtOAc and dried. HPLC investigation showed complete reduction to alcohols **1** and **4** in a ratio of 88:12, identical with authentic materials[5].

3-Amino-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**5**)

A suspension of ketone **2**[5] (4 g, 13.6 mmol) and anhydrous $AlCl_3$ (0.2 g, 1.5 mmol) in formamide (30 ml) was heated in a sealed tube at 170°C for 18 h. After cooling the mixture was diluted with EtOAc (400 ml) and washed with N HCl and H_2O (2 x). The org. phase was dried, evaporated, and the residue was crystallized from Et_2O: 3.4 g (85%), m.p. > 255°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.54 (s, 3H), 1.55 (s, 3H), 5.61 (s br, 2H), 6.26 (d, J = 1.6 Hz, 1H), 6.32 (td, J = 8.0, 8.0, 1.5 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.35-7.18 (m, 2H), 7.51 (td, J = 8.0, 8.0, 1.4 Hz, 1H).- $C_{17}H_{15}N_3O_2$ (293.3) Calcd. C 69.6 H 5.15 N 14.3 Found C 69.6 H 5.14 N 14.4.

3-Diacetylamino-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**6**)

Compound **5** (0.13 g, 0.34 mmol) was refluxed in Ac_2O (10 ml) for 4 h. The solution was evaporated and the residue purified on a silica gel column using EtOAc: 0.085 g (51%), m.p. 194-196°C (Et_2O).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.51 (s, 3H), 1.58 (s, 3H), 2.25 (s, 3H), 2.37 (s, 3H), 6.41 (td, J = 6.8, 6.8, 1.3 Hz, 1H), 6.51 (dt, J = 9.7, 1.4, 1.4 Hz, 1H), 7.11 (ddd, J = 7.0, 2.0, 0.5 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.59 (ddd, J = 8.9, 7.5, 2.0 Hz, 1H), 7.80 (dd, J = 8.4, 2.0 Hz, 1H).- $C_{21}H_{19}N_3O_4$ (377.4) Calcd. C 66.8 H 5.07 N 11.1 Found C 67.1 H 5.13 N 11.1.

4-Bromo-3-formyl-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**8**)

To an ice-cold mixture of $CHCl_3$ (30 ml) and DMF (9.6 ml, 125 mmol) PBr_3 (9.6 ml, 102 mmol) and then a solution of ketone **7**[5] (8 g, 40 mmol) in $CHCl_3$ (15 ml) were added dropwise. Stirring was continued for 30 min, then the solution was heated under reflux for an additional 7 h. The mixture was diluted with H_2O and extracted with EtOAc (2 x 100 ml). The org. phase was dried, evaporated, and the residue chromatographed (silica gel, gradient elution petroleum ether → Et_2O): 1.1 g (9%), m.p. 124-125°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.59 (s, 6H), 7.08 (d, J = 9.1 Hz, 1H), 7.90 (dd, J = 9.1, 2.0 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 9.98 (s, 1H).- IR (KBr): 2226 (C≡N), 1672 (C=O) cm^{-1}.- $C_{13}H_{10}BrNO_2$ (292.1) Calcd. C 53.4 H 3.46 Br 27.4 N 4.8 Found C 53.5 H 3.58 Br 27.7 N 4.9.

3-Formyl-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**9**)

A suspension of compound **8** (1.4 g, 4.8 mmol), 2-pyridinol (0.9 g, 9.5 mmol), and K_2CO_3 (3 g, 22 mmol) in DMF (20 ml) was stirred at 60°C for 1 h. The suspension was diluted with EtOAc and filtered. The filtrate was washed with H_2O (2 x), dried, evaporated, and the residue was purified by chromatography on silica gel using Et_2O: 0.7 g (47%) yellow crystals, m.p. 190-192°C (Et_2O).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.65 (s, 3H), 1.70 (s, 3H), 6.47 (td, J = 6.5, 1.6 Hz, 1H), 6.58 (d, J = 9.9 Hz, 1H), 7.12 (m, 2H), 7.72-7.59 (m, 2H), 7.85 (dd, J = 9.9, 2.0 Hz, 1H), 9.35 (s, 1H).- IR (KBr): 2220 (C≡N), 1687 (C=O), 1666 (C=O) cm^{-1}.- $C_{18}H_{14}N_2O_3 \cdot 0.25\ H_2O$ (310.8) Calcd. C 69.5 H 4.71 N 9.0 Found C 69.3 H 4.68 N 8.9.

Aldehyde **9** *by oxidation of* **10**

To a -70°C cold solution of compound **10**[4] (1.5 g, 5.1 mmol) in dry THF (75 ml) MeLi in Et_2O (5%; 3.3 ml, 5.3 mmol) was slowly added by syringe under N_2. The resulting dark solution that was stirred at low temp. for 1 h turned bright on introducing O_2-gas for 30 min. After quenching with MeOH (10 ml) the mixture was evaporated and the residue chromatographed to give compound **9** (50 mg, 3%).

4-(1,2-Dihydro-2-oxo-1-pyridyl)-3-hydroxymethyl-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**11**)

$NaBH_4$ (0.2 g, 5.3 mmol) was added to a solution of aldehyde **9** (0.3 g, 1 mmol) in MeOH (20 ml). The mixture was stirred at room temp. for 30 min and evaporated. The residue was taken up in EtOAc, washed with H_2O (2 x), and dried. Filtration and evaporation gave alcohol **11** as a colorless solid: 0.1 g (33%), m.p. 190-192°C (Et_2O).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.70 (s, 6H), 2.90 (br, 1H), 3.95 (d, J = 12.5 Hz, 1H), 4.10 (d, J = 12.5 Hz, 1H), 6.37 (td, J = 6.5, 1.3 Hz, 1H), 6.82-6.72 (m, 2H), 6.96 (d, J = 9.4 Hz, 1H), 7.04 (dd, J = 7.0, 1.8 Hz, 1H), 7.62-7.44 (m, 2H).- $C_{18}H_{16}N_2O_3 \cdot 0.25\ H_2O$ (312.9) Calcd. C 69.1 H 5.33 N 9.0 Found C 69.4 H 5.26 N 9.0.

4-(1,2-Dihydro-2-oxo-1-pyridyl)-3-hydroxyiminomethyl-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**12**) *and 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2H-1-benzopyran-3,6-dicarbonitrile* (**13**)

A solution of aldehyde **9** (0.46 g, 1.48 mmol), hydroxylamine hydrochloride (0.132 g, 1.9 mmol), and sodium formate (0.184 g, 2.7 mmol) in formic acid (4 ml) was stirred at room temp. for 4 h. Water (10 ml) was added and the resulting solid **12** collected by filtration: 0.285 g (60%), m.p. 276-278°C (MeOH).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.72 (s, 6H), 6.42 (t, J = 5.5 Hz, 1H), 6.56 (d, J = 9.4 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.32 (s, 1H), 7.78-7.48 (m, 3H), 11.84 (s, 1H).- $C_{18}H_{15}N_3O_3$ (321.3) Calcd. C 67.3 H 4.71 N 13.1 Found C 66.9 H 5.09 N 13.2.- Alternatively, heating the above reaction mixture under reflux for 30 min afforded compound **13** (77%), m.p. 199-201°C (diisopropyl ether).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.69 (s, 6H), 6.50 (t, J = 5.5 Hz, 1H), 6.59 (d, J = 8.9 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.77-7.57 (m, 2H), 7.89 (dd, J = 7.4, 1.7 Hz, 1H).- $C_{18}H_{13}N_3O_2$ (303.3) Calcd. C 71.3 H 4.33 N 13.9 Found 71.3 H 4.40 N 13.9.- Similar treatment of aldehyde **8** yielded compound **14**: m.p. 160-162°C (diisopropyl ether).- $C_{13}H_9BrN_2O$ (289.1) Calcd. C 54.0 H 3.14 Br 27.6 N 9.7 Found C 53.9 H 3.24 Br 27.9 N 9.6.- Treatment of **14** in analogy to the procedure described for **9** gave **13** in 10% yield.

trans-3-Chloro-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**16**)

Mesylation of chromanol **1**[5] using mesyl chloride in pyridine afforded **15** in 92% yield, m.p. 193-195°C (diisopropyl ether).- $C_{18}H_{18}N_2O_5S$ (374.4) Calcd. C 57.7 H 4.86 N 7.5 S 8.6 Found C 57.7 H 4.99 N 7.4 S 8.5.- Compound **15** (15 g, 40 mmol) and LiCl (17 g, 0.4 mol) in DMF (1 l) were stirred at 100°C overnight. The mixture was poured into H_2O, extracted with EtOAc, and the org. phase dried and evaporated. Purification: chromatography on silica gel with CH_2Cl_2/EtOAc mixtures, gradient elution technique. The nonpolar fractions were combined to give compound **16**: 500 mg (4%), m.p. 227-228°C (diisopropyl ether).- ^{1}H-NMR of the predominately existing conformation ($CDCl_3$): δ (ppm) = 1.52 (s, 3H), 1.60 (s, 3H), 4.12 (d, J = 11.2 Hz, 1H), 6.23 (td, J = 6.8, 1.5 Hz), 6.69 (d, J = 11.2 Hz, 1H), 6.72 (dd, J = 9.3, 1.3 Hz, 1H), 6.86 (dd, J = 7.0, 3.0 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 7.06 (m, 1H), 7.38 (m, J = 8.8, 6.8, 2.0 Hz, 1H), 7.49 (dd, J = 8.5, 2.2 Hz, 1H).- $C_{17}H_{15}ClN_2O_2$ (314.8) Calcd. C 64.9 H 4.81 Cl 11.3 N 8.9 Found C 64.7 H 4.80 Cl 11.6 N 8.8.

cis-3-Chloro-3,4-dihydro-4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)oxy]-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (**19**)

Compound **19** was prepared in an analogous manner to that described from chromanol **17**[13] *via* tosylate **18**. Compound **18**: m.p. 89-91°C (Me_2CHOH).- $C_{24}H_{23}N_3O_6S \cdot C_3H_8O$ (541.7) Calcd. C 59.9 H 5.78 N 7.8 S 5.9 Found C 60.1 H 5.90 N 7.6 S 6.0.- Compound **19**: m.p. 198-200°C (diisopropyl ether).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.50 (s, 3H), 1.57 (s, 3H), 3.59 (s, 3H), 5.13 (d, J = 4.2 Hz, 1H), 6.22 (d, J = 4.2 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.04 (d, 9.9 Hz, 1H), 7.41 (d, J = 9.7 Hz, 1H), 7.73 (dd, J = 8.6, 1.9 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H).- $C_{17}H_{17}ClN_3O_3 \cdot 0.5\ H_2O$ (354.8) Calcd. C 57.5 H 4.84 Cl 10.0 N 11.8 Found C 57.7 H 4.60 Cl 9.9 N 11.6.

3-Bromo-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-2H-1-benzopyran-6-carbonitrile (**21**)

Bromine (0.5 ml, 9.8 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of compound **20**[14] (2.68 g, 10 mmol) in CH_2Cl_2 (40 ml) and the reaction mixture was stirred for 30 min at room temp. The solvent was evaporated and the residue chromatographed on silica gel (CH_2Cl_2 → EtOAc). The polar fractions were combined to give **21** (2.1 g, 60%), m.p. 172-173°C ($Me_2CH)_2O$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.57 (s, 3H), 1.58 (s, 3H), 2.13 (m, 1H), 2.28 (m, 1H), 2.34 (m, 1H), 2.57 (m, 1H), 3.53-3.62 (m, 2H), 7.07 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.5, 2.0 Hz, 1H).- $C_{16}H_{15}BrN_2O_2 \cdot 0.25\ H_2O$ (351.7) Calcd. C 54.6 H 4.45 Br 22.7 N 8.0 Found C 54.7 H 4.51 Br 23.1 N 7.9.

Crystal Data

3: $C_{17}H_{13}ClN_2O_3$; M = 328.8; triclinic; P1 (no. 2); *a* = 1009.58 (8) pm; *b* = 1029.9 (1) pm; *c* = 820.8 (1) pm; α = 108.19° (1); β = 96.29° (1); γ = 87.12° (1); V = 805.8 (1) x 10^6 pm^3; Z = 2; ρ_x = 1.355 g cm^{-3}; μ(Cu Kα) = 22.534 cm^{-1}; F(000) = 340; no. of reflections with I ≥ 3σ(I) = 2553; no. of refinement parameters = 261; final R values, R = 0.048; R_w = 0.046.

16: $C_{17}H_{15}ClN_2O_2$; M = 314.8; monoclinic; $P2_1/c$ (no. 14); *a* = 1618.4 (3) pm; *b* = 940.0 (2) pm; *c* = 1069.9 (2) pm; α = 90°; β = 101.34° (2); γ = 90°; V = 1595.9 (2) x 10^6 pm^3; Z = 4; ρ_x = 1.310 g cm^{-3}; μ(Cu Kα) = 22.026 cm^{-1}; F(000) = 656; no. of reflections with I ≥ 3σ(I) = 2279; no. of refinement parameters = 245; final R values, R = 0.046; R_w = 0.042.

21: $C_{16}H_{15}BrN_2O_2$; M = 347.2; triclinic; P1 (no. 2); *a* = 626.1 (1) pm; *b* = 901.4 (1) pm; *c* = 1387.2 (1) pm; α = 104.61° (1); β = 94.32° (1); γ = 98.82° (1); V = 743.3 (2) x 10^6 pm^3; Z = 2; ρ_x = 1.551 g cm^{-3}; μ(Cu Kα) = 38.355 cm^{-1}; F(000) = 352; no. of reflections with I ≥ 3σ(I) = 2687; no. of refinement parameters = 236; final R values, R = 0.032; R_w = 0.035.

Further X-ray crystallographic data, including positional parameters, bond distances, bond angles, and anisotropic displacement parameter expressions, for **3**, **16**, and **21** (29 pages) are available from the authors.

Antihypertensive Studies in Conscious Spontaneously Hypertensive Rats

Compounds were tested for antihypertensive activity in conscious spontaneously hypertensive male rats (280-340 g; blood pressure > 170 mm Hg; origin: Okamoto strain). Mean arterial pressure was recorded directly *via* an aortic catheter in unrestrained animals. A HSE setup (Statham pressure transducer, Watanabe recorder, HSE oscilloscope) was used for the recording of arterial blood pressure. 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. For each compound 1 mg/kg was administered orally as a screening dose. The substances were suspended in 5% gum arabic and administered orally by gavage.

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