was removed by filtration through Celite, and solvent was removed in vacuo. Labile tritium was removed by codistillation with methanol (3 × 2 mL) under reduced pressure. Analysis of the crude product (287 mCi) by TLC [Whatman LK6F silica gel, $CHCl_3/CH_3OH$ (90:10), developed 2 × 15 cm] indicated a purity of 52% ($R_f$ = 0.33) with the remaining activity in higher $R_f$ components. A 114 mCi portion of this material was purified by preparative TLC using the above system on four 5 × 20 cm plates (analytical grade). The product was recovered by extraction with methanol and purified again by the same procedure to remove a small amount of impurity at $R_f$ = 0.4. A total of 41.6 mCi of pure [$^3$H]-**5** was obtained, with a specific activity of 16.2 Ci mmol$^{-1}$ (spectrophotometric determination in 95% ethanol using $\epsilon_{254}$ = 1.11 × 10$^4$).

Radiochemical purity of this material was determined to be ≥98% by TLC and HPLC [HPLC system: Varian 5500 instrument, Whatman Partisil 5, 4.6 × 250 mm column, mobile phase 13% 80:20:05 $CHCl_3$/MeOH/$Et_3N$ in $CHCl_3$, flow rate 1.0 mL min$^{-1}$, Varian UV-200 UV detector, Radiomatic HP30 Flo-One radiodetector. $t_R$ for compound **5** = 11.5 min, $t_R$ for compound **9** = 10.4 min].

**Binding Methods.** Mouse neuroblastoma-glioma cells (NG 108-15 cell line) were harvested and centrifuged at 900*g* at 4 °C for 10 min. The resulting pellet was resuspended in 10 mL of 20 mM Tris-HCl, 154 mM NaCl, pH 7.5 solution and homogenized with a Polytron (setting 9, 2 × 15 s). The suspension was spun as before. The final supernatant was diluted with Tris-HCl-NaCl buffer to yield 50 mg tissue/mL and stored for later use at −60 °C.

Cell suspension (150 μL) was incubated at 37 °C for 15 min with 0.1–10 nM of radioligand in 20 mM Tris-HCl, 154 mM NaCl, pH 7.5 solution in a final volume of 250 μL. Nonspecific binding was determined by 10 μM zacopride. Incubations were terminated by rapid filtration through 0.2% PEI-soaked borosilicate filtermats and washed with ice-cold Tris-HCl-NaCl buffer (3 × 5 mL). Filters were soaked overnight in 4 mL of Ecolume, and the retained radioactivity was determined with an LKB liquid-scintillation counter. Data were analyzed with the Lundon 1 software program.

# Variation in the Aromatic Ring of Cromakalim: Antihypertensive Activity of Pyranopyridines and 6-Alkyl-2*H*-1-benzopyrans

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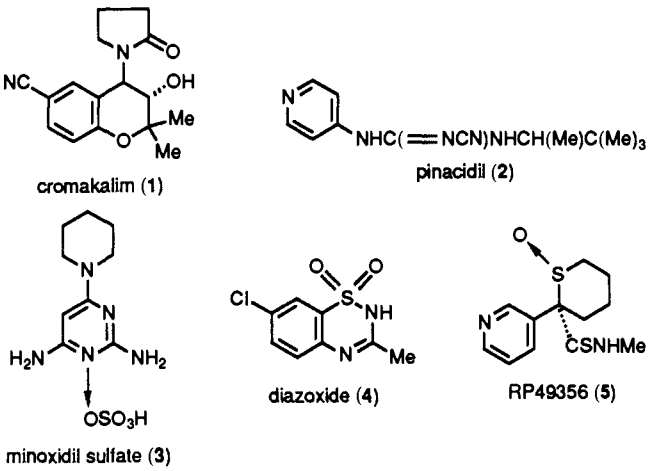
The synthesis and antihypertensive activity in the spontaneously hypertensive rat of two new series of analogues related to cromakalim (1) are described. In the first series, where the benzopyran nucleus has been replaced by a pyranopyridine nucleus, the position of the nitrogen atom has been found to be critical for activity, and the most potent compounds are the pyrano[3,2-*c*]pyridines. In the second series, where the powerful electron-withdrawing cyano group of compound 1 has been replaced by alkyl and phenyl groups, the order of antihypertensive potency is ethyl, isopropyl, *tert*-butyl > propyl, cyclopentyl > methyl > phenyl.

Since the discovery[1] that cromakalim (1) exerts its antihypertensive effect by a mechanism involving the enhanced outward flow of potassium ions through, and hyperpolarization of, the membranes of smooth muscle cells, several other compounds have been found to possess similar properties.

Thus, the established vasodilator pinacidil (2), together with minoxidil sulfate (3), diazoxide (4), and more recently RP49356 (5) (see Chart I) have all been reported[2] to be potassium-channel activators.

In previous papers we have described the structure–activity relationships pertaining to compound 1 and its cyclic amido[3] and acyclic amido[4] analogues, deduced from oral administration to spontaneously hypertensive rats (SHR). One of the conditions that was required for optimum activity was the presence of a powerful electron-withdrawing group such as nitro or cyano at position C(6) of the benzopyran ring. Mapping of two-dimensional electrostatic potentials of compound 1 and its analogues containing strong electron-withdrawing groups led us to synthesize pyrano[3,2-*c*]pyridine 7 (see Table I), as this ring system was shown to be electronically similar to the 6-cyanobenzopyran ring in these studies. The good blood pressure lowering activity of compound 7 confirmed the theoretical approach, and certain analogues have been prepared (Table I) to establish structure–activity relationships in this first series of compounds.[5]

**Chart I**



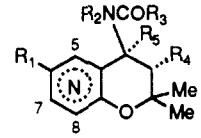

† Present address: Glaxochem Ltd., Ulverston, Cumbria, England.

‡ Present address: Merck, Sharp, and Dohme Research Laboratories Ltd., Neuroscience Research Centre, Terlings Park, Harlow, England.

(1) Hamilton, T. C.; Weir, S. W.; Weston, A. H. *Br. J. Pharmacol.* **1986**, *88*, 103.
(2) Robertson, D. W.; Steinberg, M. I. *Annual Reports in Medicinal Chemistry*; Allen, R. C., Ed.; Academic Press: San Diego, 1989; Vol. 24, p 91.
(3) 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.
(4) Ashwood, V. A.; Cassidy, F.; Coldwell, M. C.; Evans, J. M.; Hamilton, T. C.; Howlett, D. R.; Smith, D. M.; Stemp, G. *J. Med. Chem.*, in press.

0022-2623/90/1833-3023$02.50/0 

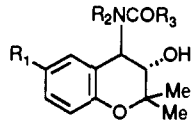
**Table I.** *trans*-3,4-Dihydro-4-(2-oxopyrrolidin-1-yl)-2*H*-pyranopyridin-3-ols and Analogues




| compd | $R_1$ | N-posn | $R_2$ | $R_3$ | $R_4$ | $R_5$ | % yield | mp, °C | recryst solv[a] | formula | anal.[b] | dose, mg/kg po | % max fall in[c] bp ± SEM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[d] | CN | | $-(CH_2)_3-$ | | OH | H | | | | | | 0.1 | 13 ± 5 |
| | | | | | | | | | | | | 0.3 | 39 ± 4 |
| | | | | | | | | | | | | 1.0 | 47 ± 1 |
| 6 | H | 5 | $-(CH_2)_3-$ | | OH | H | 31 | 214–215 | E-P | $C_{14}H_{18}N_2O_3$ | C,H,N | 10.0 | 15 ± 3 |
| 7 | | 6 | $-(CH_2)_3-$ | | OH | H | 12 | 253 | E | $C_{14}H_{18}N_2O_3$ | C,H,N | 1.0 | 39 ± 7 |
| | | | | | | | | | | | | 3.0 | 41 ± 4 |
| 8 | H | 7 | $-(CH_2)_3-$ | | OH | H | 21 | 221–225 | E-M | $C_{14}H_{18}N_2O_3$ | H,N;C[e] | 1.0 | 7 ± 3 |
| | | | | | | | | | | | | 10.0 | 41 (2) |
| 9 | H | 8 | $-(CH_2)_3-$ | | OH | H | 30 | 202–203 | E-P | $C_{14}H_{18}N_2O_3$ | C,H,N | 10.0 | 5 ± 3 |
| 10 | | 6 | $-(CH_2)_4-$ | | OH | H | 16 | 241–243 | E | $C_{15}H_{20}N_2O_3$ | C,H,N | 0.1 | 24 ± 4 |
| | | | | | | | | | | | | 0.3 | 55 ± 4 |
| | | | | | | | | | | | | 1.0 | 56 ± 4 |
| 11 | O | 6 | $-(CH_2)_4-$ | | OH | H | 75 | 290–291 | E-M | $C_{15}H_{20}N_2O_4$ | C,H,N | 0.3 | 39 ± 0 |
| | | | | | | | | | | | | 1.0 | 68 ± 1 |
| 12 | | 6 | $-(CH_2)_4-$ | | bond | | 31 | 108–113 | E-P | $C_{15}H_{18}N_2O_2$ | C,H,N | 1.0 | 14 ± 4 |
| | | | | | | | | | | | | 3.0 | 37 ± 3 |
| 13 | | 6 | H | Me | OH | H | 32 | 208–210 | E | $C_{12}H_{16}N_2O_3$ | C,H,N | 0.3 | 14 ± 2 |
| | | | | | | | | | | | | 1.0 | 43 ± 5 |

[a] E = EtOAc, M = MeOH, P = pentane. [b] Analyses for the elements indicated were witin ±0.4% of the theoretical values. [c] Systolic blood pressure was measured indirectly at intervals from 1 to 6 h in groups of six SH rats per dose level. On occasion pulses were determined from only (*n*) SH rats. [d] See ref 6. [e] C: calcd, 64.11; found, 63.67.

**Table II.** *trans*-6-Alkyl-3,4-dihydro-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-ols and Analogues



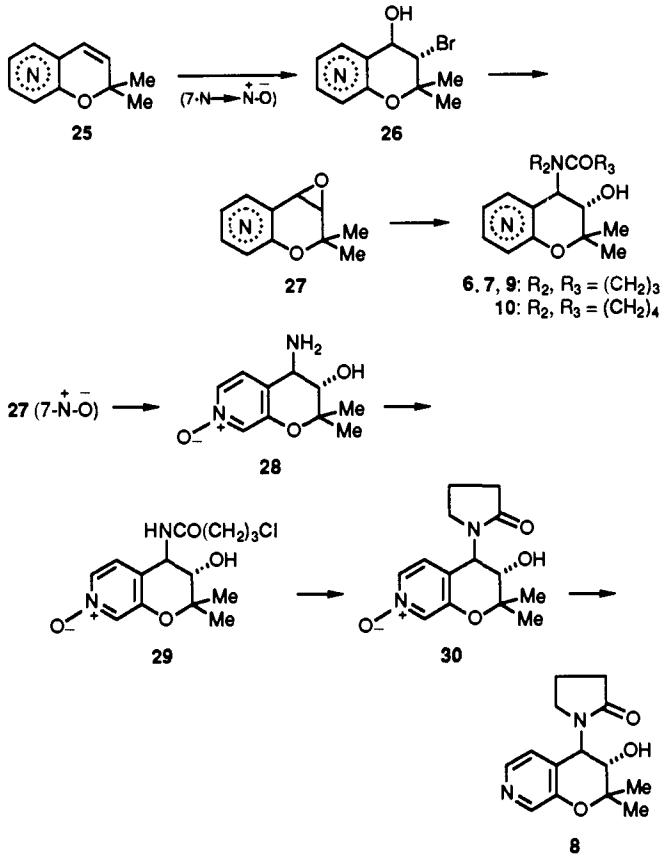

| compd | $R_1$ | $R_2$ | $R_3$ | % yield | mp, °C | recryst solv[a] | formula | anal.[b] | dose, mg/kg po | % max fall in[c] bp ± SEM |
|---|---|---|---|---|---|---|---|---|---|---|
| 14 | $CF_3$ | $-(CH_2)_3-$ | | 44 | 181–182 | E | $C_{16}H_{18}NO_3F_3$ | H,N;C[d] | 0.1 | 17 ± 2 |
| | | | | | | | | | 0.3 | 26 ± 4 |
| | | | | | | | | | 1.0 | 43 ± 5 |
| 15[e] | H | $-(CH_2)_3-$ | | | | | | | 10.0 | 9 ± 4 |
| 16 | Me | $-(CH_2)_3-$ | | 35 | 187–188 | E-P | $C_{16}H_{21}NO_3$ | C,H,N | 3.0 | 12 ± 6 |
| | | | | | | | | | 10.0 | 49 ± 7 (4) |
| 17 | Me | $-(CH_2)_4-$ | | 15 | 162–164 | E | $C_{17}H_{23}NO_3$ | C,H,N | 0.3 | 16 ± 5 |
| | | | | | | | | | 1.0 | 33 ± 2 |
| | | | | | | | | | 3.0 | 56 ± 2 |
| 18 | Et | $-(CH_2)_3-$ | | 49 | 154–163 | E-PE | $C_{17}N_{23}NO_3$ | C,H,N | 0.3 | 11 ± 4 |
| | | | | | | | | | 1.0 | 54 ± 2 |
| 19 | $Me(CH_2)_2$ | $-(CH_2)_3-$ | | 15 | 139–140 | E | $C_{18}H_{25}NO_3$ | C,H,N | 1.0 | 17 ± 7 |
| | | | | | | | | | 3.0 | 42 ± 7 (5) |
| 20 | $Me_2CH$ | $-(CH_2)_3-$ | | 32 | 167–173 | E | $C_{18}H_{25}NO_3$ | C,H,N | 0.3 | 17 ± 4 |
| | | | | | | | | | 1.0 | 36 ± 5 |
| | | | | | | | | | 3.0 | 60 (2) |
| 21 | $Me_3C$ | $-(CH_2)_3-$ | | 16 | 227–228 | E-PE | $C_{19}H_{27}NO_3$ | C,H,N | 0.3 | 9 ± 5 |
| | | | | | | | | | 1.0 | 39 ± 9 |
| | | | | | | | | | 3.0 | 49 ± 6 (4) |
| 22 | *c*-$C_5H_9$ | $-(CH_2)_3-$ | | 27 | 179–184 | E | $C_{20}H_{27}NO_3$ | C,H,N | 1.0 | 24 ± 2 |
| | | | | | | | | | 10.0 | 66 ± 2 (3) |
| 23 | Ph | $-(CH_2)_3-$ | | 10 | 217–220 | E-P | $C_{21}H_{23}NO_3$ | C,H,N | 3.0 | 14 ± 5 |
| | | | | | | | | | 10.0 | 20 ± 2 (4) |
| 24 | Me | H | Me | 21 | 188–190 | E | $C_{14}H_{19}NO_3 \cdot 0.25H_2O$ | C,H,N | 0.3 | 9 ± 4 |
| | | | | | | | | | 3.0 | 20 ± 6 |

[a] E = EtOAc, P = pentane, PE = 60–80 °C petroleum ether. [b,c] See footnotes *b* and *c* of Table I. [d] C: calcd, 58.36; found, 59.63. [e] See ref 3.

In accordance with the requirement for a strong electron-withdrawing group, 6-$CF_3$ compound **14** showed good activity (Table II), while the unsubstituted compound **15** did not lower blood pressure at the top dose investigated (10 mg/kg).[3] However, in stark contrast to these results, the 6-methyl compound **16** had surprisingly good activity at 10 mg/kg, producing a fall of approximately 50%. This result prompted an investigation of a series of 6-alkyl

(5) Evans, J. M.; Cassidy, F.; Stemp, G. Partly presented at the 197th ACS National Meeting, Dallas, Texas, 1989, Symposium on Potassium Channels.

**Scheme I**

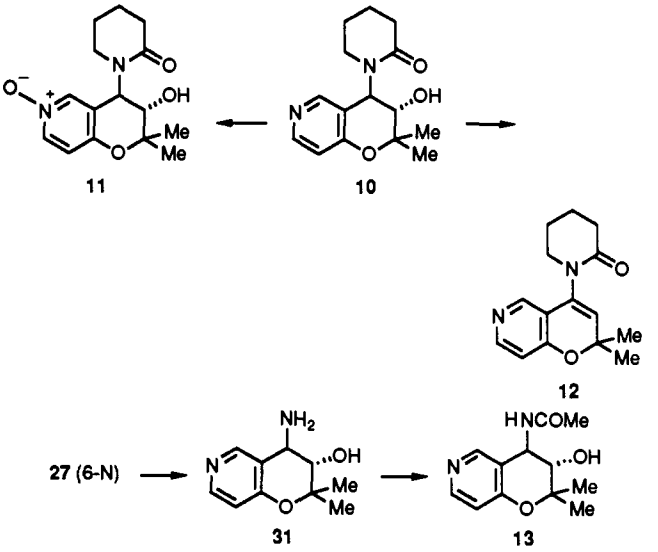



analogues of compound **16** (see Table II).[5]

## Chemistry

Synthesis of pyranopyridines **6–10** (see Table I) required as starting materials the appropriate 2,2-dimethyl-2*H*-pyranopyridines **25**, the syntheses of which have been reported recently.[6] Thus by the established route for compound **1**, compounds **6**, **7**, **9**, and **10** were prepared (Scheme I) via bromohydrin **26** and epoxide **27**. Compounds **6**, **7**, and **9** were obtained by the action of pyrrolidone and compound **10** was obtained by the action of piperidone on the appropriate epoxide **27** in the presence of NaH base. The synthesis of compound **8** required changes in strategy as treatment of pyrano[2,3-*c*]pyridine **25** (7-N) with moist NBS failed to give a bromohydrin. However, conversion of pyrano[2,3-*c*]pyridine **25** to its *N*-oxide with *m*-CPBA followed by treatment with moist NBS gave bromohydrin **26** (7-$N^+$–$O^-$). Conversion of bromohydrin **26** (7-$N^+$–$O^-$) to epoxide **27** (7-$N^+$–$O^-$) was followed by treatment with ammonia and amino alcohol **28** acylated with chlorobutyryl chloride to give (chlorobutyryl)amino compound **29**, as epoxide **27** (7-$N^+$–$O^-$) failed to react with pyrrolidone under the usual conditions described for the preparation of compounds **6**, **7**, and **9**. Ring closure under basic conditions yielded pyrrolidone **30**. Deoxygenation of **30** with hexachlorodisilane[7] provided the required compound **8**. Treatment of compound **10** with *m*-CPBA gave the *N*-oxide **11**, and dehydration of **10** with NaH gave the dihydro compound **12** (Scheme II). Finally, the pyrano[3,2-*c*]-pyridine epoxide **27** (6-N) was treated with ammonia, and amino alcohol **31** was acylated with acetyl chloride to give compound **13** (Scheme II).

**Scheme II**




The synthesis of the 6-$CF_3$ compound **14**, the 6-alkyl compounds **16–22**, and the 6-phenyl compound **23** also followed the established synthetic route (see Scheme III) devised for compound **1**. Thus the appropriate phenols were alkylated with 3-chloro-3-methylbut-1-yne under phase-transfer catalytic conditions to furnish 3-methyl-3-(4-substituted-phenoxy)-but-1-ynes **32**. These were thermally cyclized in boiling *o*-dichlorobenzene to give 6-substituted chromenes **33** as oils, which were characterized by NMR spectroscopy before being converted directly into bromohydrins **34** by treatment with aqueous NBS. Action of base yielded epoxides **35** which were treated with the appropriate cyclic amide and 1 equiv of NaH to give compounds **14** and **16–23** (Table II). The 6-methyl epoxide **35** (R = Me)[8] was converted to amino alcohol **36** and reacted with acetyl chloride to give compound **24**.

## Results and Discussion

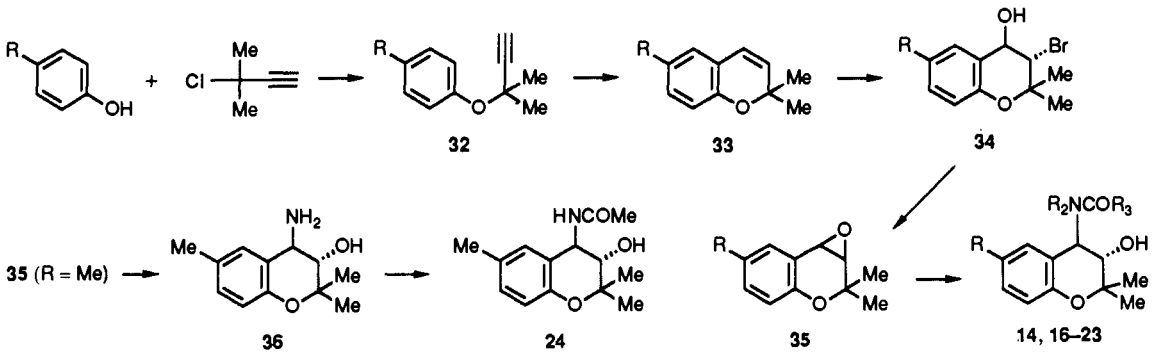
Compounds were evaluated for oral antihypertensive activity in the SHR. Systolic blood pressure, recorded from the tail, was determined before dosing and at various time intervals during the ensuing 6 h. Maximum falls in blood pressure obtained for all the compounds (Tables I and II) occurred at 1–4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

In the four isomeric pyranopyridine analogues **6–9**, structure–activity relationships are in line with previous results obtained[3] when variation of the position of substituents in the aromatic ring was studied and in agreement with the predictions from the modeling of two-dimensional electrostatic potentials. Thus the most potent compound (Table I) is pyrano[3,2-*c*]pyridine compound **7**, while the pyrano[2,3-*c*]pyridine compound **8** only possessed reasonable activity at the highest dose. The pyrano[3,2-*b*]- and -[2,3-*b*]pyridines compounds **6** and **9**, respectively, showed little activity at the highest dose employed. In the potent pyrano[3,2-*c*]pyridine series the homologous piperidone compound **10** showed enhanced activity over pyrrolidone **7**, a differential in activity first observed[3] for the piperidone analogue of compound **1**.

Preparation of the *N*-oxide of compound **10** resulted in an analogue, **11**, of similar potency, but the unsaturated variant **12** of compound **10** was found to be less active, thus illustrating again the variability in comparative activities

(6) Evans, J. M.; Stemp, G. *Synth. Commun.* **1988**, *18*, 1111.
(7) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 2788.
(8) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1983**, *26*, 1582.

**Scheme III**




of 3-hydroxy compounds and dehydro compounds that we have reported previously.[3]

In accord with the earlier work, compound **14** (Table II) which contains the strong electron-withdrawing $CF_3$ group at C(6) showed good activity, being approximately equiactive with compound **1**. Unsubstituted compound **15** was inactive at the dose tested, but 6-methyl compound **16**, which is similar in shape but not in electronic effect to 6-$CF_3$ compound **14**, had surprisingly good activity at 10 mg/kg. The possibility arises that the activity of compound **16** might be ascribed to the shape and/or lipophilicity of the C(6) substituent, and that the enhanced activity of compound **14** may be due to the additional electron-withdrawing properties of the $CF_3$ substituent when compared with a methyl substituent. Again piperidone compound **17** showed a greater potency than pyrrolidone compound **16**, as was noted in the pyrano[3,2-*c*]pyridine series above.

Extension of the methyl group to ethyl as in compound **18** substantially enhanced the activity, but the *n*-propyl compound **19** was only about $^1/_3$ as potent as 6-ethyl compound **18**. However, introduction of branched alkyl groups gave isopropyl (**20**) and *tert*-butyl (**21**) compounds of similar potency to the ethyl compound **18**, while cyclopentyl analogue **22** was at least 3-fold less active than compound **18**. Replacement of the alkyl group by a phenyl ring (compound **23**) reduced activity to modest levels.

Representative acyclic amido analogues, 4-acetylamino compounds **13** (Table I) and **24** (Table II), have been prepared in the pyrano[3,2-*c*]pyridine and the 6-alkyl series, respectively. These compounds compare very favorably in potency with the equivalent pyrrolidones **7** and **16**, respectively. Such equivalence has been reported previously[4] for the 4-(acetylamino) analogue of compound **1**.

## Experimental Section

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian EM 360A at 60 MHz, a Varian CFT-20 at 80 MHz, or a JEOL GX 270, and mass spectra were recorded on a VG 70-70 or 70 ZAB or a JEOL DX 303 at 70 eV, respectively, and were in agreement with the structures cited. $HF_{254}$ silica gel plates (2 mm) were used for Chromatotron chromatography (radial chromatography). Petroleum ether refers to that fraction boiling between 60 and 80 °C. Two dimensional electrostatic potential maps were generated with a modified VSS procedure[9] from partial charges calculated by the semiempirical CNDO method.[10]

**3-Methyl-3-(4-substituted-phenoxy)but-1-ynes (32).** The appropriate phenol (0.06 mol) and NaOH (0.1 mol) were added to a stirred mixture of $H_2O$ (60 mL) and $CH_2Cl_2$ (60 mL), followed by benzyltrimethylammonium hydroxide (40% in MeOH, 0.06 mol) and 3-chloro-3-methyl-but-1-yne (0.1 mol). The mixture was stirred at room temperature for 4–11 days, and the layers were separated. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was concentrated in vacuo and taken up in $Et_2O$. The solution was washed with $H_2O$, 10% NaOH, and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation gave compounds **32** in yields of 19–50%.

**2,2-Dimethyl-6-substituted-2*H*-1-benzopyrans (33).** Phenoxybutynes **32** (0.05 mol) were heated in *o*-dichlorobenzene (2 mL/g of **32**) under $N_2$ for 2–12 h. Solvent was removed under vacuum, and crude **33** was used directly or, more usually, purified by chromatography on silica gel with EtOAc as eluant in yields of 20–90%. Compound **33**, R = $C(Me)_3$: NMR ($CDCl_3$) $\delta$ 1.27 (s, $C(Me)_3$), 1.40 (s, $C(Me)_2$), 5.50 (d, $J$ = 9 Hz, H-3), 6.25 (d, $J$ = 9 Hz, H-4), 6.60 (d, $J$ = 8 Hz, H-8), 7.10 (m, H-7 and H-5).

***trans*-3-Bromo-3,4-dihydro-2,2-dimethyl-6-substituted-2*H*-1-benzopyran-4-ols (34).** To a solution of the appropriate 2,2-dimethylbenzopyran **33** (10 mmol) in DMSO (35 mL) and $H_2O$ (20 mL) was added NBS (20 mmol) and the mixture was stirred for 1 h. The solution was diluted with $H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$ and brine and dried over $MgSO_4$. Filtration and evaporation gave bromohydrins **34**, usually as oils (70–90%) which were characterized by NMR and high-resolution MS before conversion to epoxides **35**. Compound **34** (R = $Me_2CH$): NMR ($CDCl_3$) $\delta$ 1.20 (d, $J$ = 7 Hz, $Me_2CH$), 1.37 (s, $C(Me)_2$), 1.55 (s, $C(Me)_2$), 2.80 (sept, $J$ = 7 Hz, $Me_2CH$), 4.03 (d, $J$ = 9 Hz, H-3), 4.80 (m, H-4), 6.55 (d, $J$ = 8 Hz, H-8), 6.80–7.20 (m, H-5, H-7); mass spectrum, observed $M^+$ at $m/z$ 298.0563, 300.0553; $C_{14}H_{19}O_2Br$ requires 298.0568, 300.0548. Compound **34** (R = Ph): 69%; mp 135–139 °C (EtOAc–petroleum ether). Anal. ($C_{17}H_{17}O_2Br$) C, H, Br. Compound **34** (R = *c*-$C_5H_9$): 92%; mp 121–122 °C (EtOAc–petroleum ether). Anal. ($C_{16}H_{21}O_2Br$) C, H. Compound **34** (R = $^t$Bu): 18%; mp 122–123 °C (EtOAc–petroleum ether). Anal. ($C_{15}H_{21}O_2Br0.5H_2O$) C, H.

**3,4-Epoxy-3,4-dihydro-2,2-dimethyl-6-substituted-2*H*-1-benzopyrans (35).** Bromohydrins **34** (5 mmol) were stirred with KOH pellets (5 mmol) in $Et_2O$ (250 mL) at room temperature for 1–4 days. Filtration and evaporation gave epoxides **35**, which were used directly. Compound **35** (R = $Me_2CH$); NMR ($CDCl_3$) $\delta$ 1.20 (d, $J$ = 7 Hz, $Me_2CH$) overlapping 1.20 (s, $C(Me)_2$), 1.50 (s, $C(Me)_2$), 2.80 (sept, $J$ = 7 Hz, $Me_2CH$), 3.40 (d, $J$ = 4 Hz, H-3), 3.80 (d, $J$ = 4 Hz, H-4), 6.60 (d, $J$ = 8 Hz, H-8), 6.80–7.30 (m, H-5, H-7).

***trans*-4-Amido-3,4-dihydro-2,2-dimethyl-6-substituted-2*H*-1-benzopyrans (14, 16–23).** The requisite cyclic amide (5 mmol) was treated with 80% NaH (5 mmol) and the appropriate epoxide (5 mmol) in $Me_2SO$ (40 mL) with stirring under $N_2$ for 2–6 h. The reaction mixture was diluted with $H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$ and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation gave the title compounds as crude solids which were purified by chromatography and recrystallization (see Table II). Compound **14**: NMR ($CDCl_3$) $\delta$ 1.30 (s, $C(Me_2)$, 1.50 (s, $C(Me)_2$), 2.15 (m, $NCH_2CH_2$), 2.50 (m, $NCOCH_2$), 3.20 (m, $NCH_2$), 3.75 (d, $J$ = 10 Hz, H-3), 4.60 (br s, OH), 5.25 (d, $J$ = 10 Hz, H-4), 6.80 (d, $J$ = 8 Hz, H-8), 7.10 (d, $J$ = 2 Hz, H-5), 7.30 (dd, $J$ = 8, 2 Hz, H-7).

**2,2-Dimethyl-2*H*-pyrano[2,3-*c*]pyridine *N*-Oxide (25 *N*-Oxide).** To a stirred solution of 2,2-dimethyl-2*H*-pyrano[2,3-*c*]pyridine[6] (**25**, 8.64 g, 54 mmol) in $CHCl_3$ was added *m*-CPBA (9.15 g, 53 mmol) portionwise during 15 min. The solution was then boiled for 1 h, cooled, and evaporated, and the residue was

(9) Giessner-Prettre, C. *QCPE* **1974**, No. 249.
(10) Dobosh, P. A. *QCPE* **1968**, No. 141.

chromatographed on silica gel (500 g). Elution with 5% MeOH–$CHCl_3$ gave **25** (*N*-oxide) (5.96 g, 61%) as a colorless gum: NMR ($CDCl_3$) $\delta$ 1.45 (s, $C(Me)_2$), 5.73 (d, $J$ = 10 Hz, H-3), 6.27 (d, $J$ = 10 Hz, H-4), 6.87 (d, $J$ = 6 Hz, H-5), 7.75 (m, H-6, H-8).

***trans*-3-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-pyranopyridin-3-ols (26).** 2,2-Dimethyl-2*H*-pyranopyridines **25** were treated in a manner identical with that for 2*H*-1-benzopyrans **33** with aqueous NBS. The crude solids were purified by recrystallization, after optional chromatography. Compound **26** (3,2-*b*): 59%; mp 133–135 °C (radial chromatography eluted with 30% ethyl acetate–petroleum ether). Anal. ($C_{10}H_{12}NO_2Br$) C, H, N. Compound **26** (3,2-*c*): 34%; mp 140–141 °C (EtOAc–pentane). Anal. ($C_{10}H_{12}NO_2Br$) C, H, N. Compound **26** (2,3-*c* *N*-oxide): 68%; mp 185–187 °C (EtOAc–MeOH). Anal. ($C_{10}H_{12}NO_3Br$) C, H, N. Compound **26** (2,3-*b*): 89%; mp 163–165 °C (EtOAc). Anal. ($C_{10}H_{12}NO_2Br$) C, H, N.

**3,4-Epoxy-3,4-dihydro-2,2-dimethyl-2*H*-pyranopyridines (27).** Bromohydrins **26** were treated as bromohydrins **34** with $KOH/Et_2O$ to give epoxides **27**, which were used directly. Bromohydrin **26** (2,3-*c* *N*-oxide, 1.56 g, 5.5 mmol) and powdered KOH pellets (2.0 g, 36 mmol) were stirred and heated under reflux in THF (150 mL) for 4 h. The solution was cooled, filtered, and evaporated to give epoxide **27** (2,3-*c* *N*-oxide, 1.01 g, 91%) as a glass: NMR ($CDCl_3$) $\delta$ 1.31 (s, $C(Me)_2$), 1.58 (s, $C(Me)_2$), 3.51 (d, $J$ = 4 Hz, H-3), 3.88 (d, $J$ = 4 Hz, H-4), 7.20 (d, $J$ = 7 Hz, H-8), 7.75 (m, H-5, H-7), which was used directly in the preparation of compound **30**.

***trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-2*H*-pyrano[3,2-*c*]pyridin-3-ol (7).** [3,2-*c*]Epoxide **27** (0.43 g, 2.4 mmol) was added to a stirred solution of 2-pyrrolidone (0.22 mL, 2.9 mmol) in dry DMSO (10 mL) containing NaH (80 mg of 80% dispersion in oil, 2.7 mmol) under $N_2$ at room temperature. The reaction mixture was stirred for an additional 24 h. Water (100 mL) was added cautiously and the aqueous layer was extracted into EtOAc. The organic layer was washed with $H_2O$ (at pH 7) and brine and then dried over anhydrous $MgSO_4$. Filtration and evaporation, followed by radial chromatography (silica gel, gradient elution $CHCl_3$ to 20% MeOH–$CHCl_3$) and recrystallization, gave compound **3** (74 mg). Similarly prepared were compounds **6**, **9**, and **10** (using 2-piperidinone). See Table I.

***trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-2*H*-pyrano[2,3-*c*]pyridin-3-ol *N*-Oxide (30).** Epoxide **27** (2,3-*c* *N*-oxide, 1.01 g, 5.2 mmol) was dissolved in dry ethanolic ammonia (30 mL) and maintained at room temperature for 7 days. Evaporation and trituration with EtOAc gave amino alcohol **28** (0.62 g, 56%) as a pale yellow solid. A sample recrystallized from EtOAc–MeOH had mp 206–208 °C. Anal. ($C_{10}H_{14}N_2O_3$) H; C, N: calcd C, 57.13, N, 13.33; found C, 56.69, N, 12.88.

To an ultrasonicated, stirred solution of amino alcohol **28** (1.54 g, 5.0 mmol) in $CH_2Cl_2$ (600 mL) and $Et_3N$ (0.64 mL, 4.6 mmol) was added chlorobutyryl chloride (0.91 mL, 8.34 mmol). The ultrasonication and stirring were continued for 1 h. The solution was evaporated and the residue was chromatographed on silica gel (200 g) and eluted with a gradient of $CHCl_3$ to 10% MeOH–$CHCl_3$ to give compound **29** (1.0 g, 43%). To the (chlorobutyryl)amino compound **29** (487 mg, 1.55 mmol) dissolved in dry DMSO (10 mL) and dry THF (10 mL) was added 80 NaH (50 mg, 1.7 mmol), and the mixture was stirred for 16 h at room temperature. Water was added cautiously, and the resulting solution was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to give a solid which was recrystallized from EtOAc–MeOH to give compound **30** (135 mg, 31%): mp 268–271 °C. Anal. ($C_{14}H_{18}N_2O_4$) H, N; C: calcd, 60.42; found, 59.85.

***trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-2*H*-pyrano[2,3-*c*]pyridin-3-ol (8).** To a stirred solution of compound **30** (0.24 g, 0.9 mmol) in $CH_2Cl_2$ (200 mL) was added $Si_2Cl_6$[7] (0.4 mL, 2.3 mmol) in $CH_2Cl_2$ (20 mL) dropwise under $N_2$. The mixture was stirred for 1 h before addition of a 10% aqueous NaOH solution (0.5 mL). The mixture was stirred for 10 min and evaporated to dryness. Extraction with $CHCl_3$ and with MeOH and evaporation of the mixture gave a gum which was purified with radial chromatography (gradient elution $CHCl_3$ to 10% MeOH–$CHCl_3$) to give title compound **8** (0.11 g) (see Table I).

***trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxopiperidinyl)-2*H*-pyrano[3,2-*c*]pyridin-3-ol *N*-Oxide (11).** A solution of compound **10** (0.1 g, 0.36 mmol) and *m*-CPBA (125 mg, 0.72 mmol) in $CHCl_3$ was heated under reflux for 1.5 h. The reaction mixture was cooled and evaporated and the residue was radially chromatographed with $CHCl_3$ to 10% MeOH–$CHCl_3$ in a gradient elution to give a gum which was recrystallized to give compound **11** (70 mg) (see Table I).

**2,2-Dimethyl-4-(2-oxopiperidinyl)-2*H*-pyrano[3,2-*c*]-pyridine (12).** Compound **10** (0.4 g, 1.5 mmol) and NaH (88 mg of 80% dispersion in oil, 2.9 mmol) were boiled in dry xylene (35 mL) under $N_2$ for 2.5 h. The reaction mixture was cooled, and $H_2O$ was added cautiously and the solution was evaporated to give a gum which was radially chromatographed with $CHCl_3$ to 25% MeOH–$CHCl_3$ in a gradient elution to give a solid which was recrystallized to give compound **12** (86 mg) (see Table I).

***trans*-4-(Acetylamino)-3,4-dihydro-2,2,6-trimethyl-2*H*-1-benzopyran-3-ol (24).** Epoxide **35** (R = Me, 7.0 g, 0.037 mol) was dissolved in 0.88 M $NH_4OH$ solution (90 mL, 2.3 mmol) and EtOH (160 mL) and stirred at room temperature for 5 days. Evaporation gave crude amino alcohol **36** (7.0 g, 92%). To this amino alcohol (**36**; 1.0 g, 4.8 mmol) and $Et_3N$ (0.67 mL, 4.8 mmol) dissolved in $CH_2Cl_2$ (60 mL) was added acetyl chloride (0.34 mL, 4.8 mmol) dropwise with stirring at room temperature. The reaction mixture was stirred for 3 h and then washed with $H_2O$ and brine and dried over anhydrous $MgSO_4$. The solution was filtered and evaporated and the residue was radially chromatographed with a 30% pentane–EtOAc to EtOAc gradient elution, and the crude product was recrystallized to give compound **24** (0.25 g) (see Table II).

In a similar manner, ***trans*-4-(acetylamino)-3,4-dihydro-2,2-dimethyl-2*H*-pyrano[3,2-*c*]pyridin-3-ol (13)** was prepared from amino alcohol **31** (see Table I).

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

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

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

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

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