Conformational and Steric Modifications of the Pyran Ring of the Potassium-Channel Activator Cromakalim

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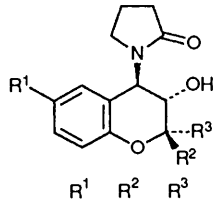
The syntheses of analogues of the novel smooth muscle relaxant cromakalim, in which the C-2 methyl groups have been successively replaced by hydrogen, are described and the relative stereochemistry of the two corresponding, isomeric monomethyl compounds, unambiguously assigned by ^{1}H NMR spectroscopic techniques. Single-crystal X-ray analysis of the 2α-monomethyl compound showed that it existed in a distorted half-chair conformation in the solid state and confirmed the relative orientation of the C-2, C-3 and C-4 substituents. The 2β-Me isomer appeared to exist in a single conformation in solution, with the pyran ring adopting a half-chair conformation and with all the substituents in this ring occupying a pseudoequatorial position. The solution behaviour of the 2α-Me isomer is more complex, however, although it seems likely to exist as a distorted half-chair conformer similar to that found in the solid state. The syntheses of two related benzoxepines are also described. All compounds were less potent than cromakalim itself, which is consistent with the view that dimethyl substitution at C-2 is essential for optimal activity.

Continued interest in the utility of cromakalim **1**† and other potassium-channel activators as novel smooth-muscle relaxants has stimulated considerable effort aimed both at identifying other compounds acting by a similar mechanism[1] and at elucidating those structural features that are essential for biological activity.[2] In addition to the known modifications at positions 1,3 and 4 and within the aromatic ring,[3-8] It has been recognised for some time that the smooth-muscle relaxant activity is tolerant of moderate steric increase at position 2, but the effects of steric reduction are less clear.[9] As part of a systematic study therefore, we have prepared a variety of C-2-modified analogues of cromakalim **1** in an attempt to rationalise the effects of steric and conformational change in the pyran ring system. In particular, we have investigated the sequential removal of one or both methyl substituents at C-2 and have prepared and unambiguously assigned the two stereoisomers of the monomethyl compounds **3** and **4**. As part of our studies, we also investigated the benzoxepine **33** and its 2,2-dimethyl homologue **41**, which have displayed an interesting reversal of biological activity compared with that observed in the benzopyran series.



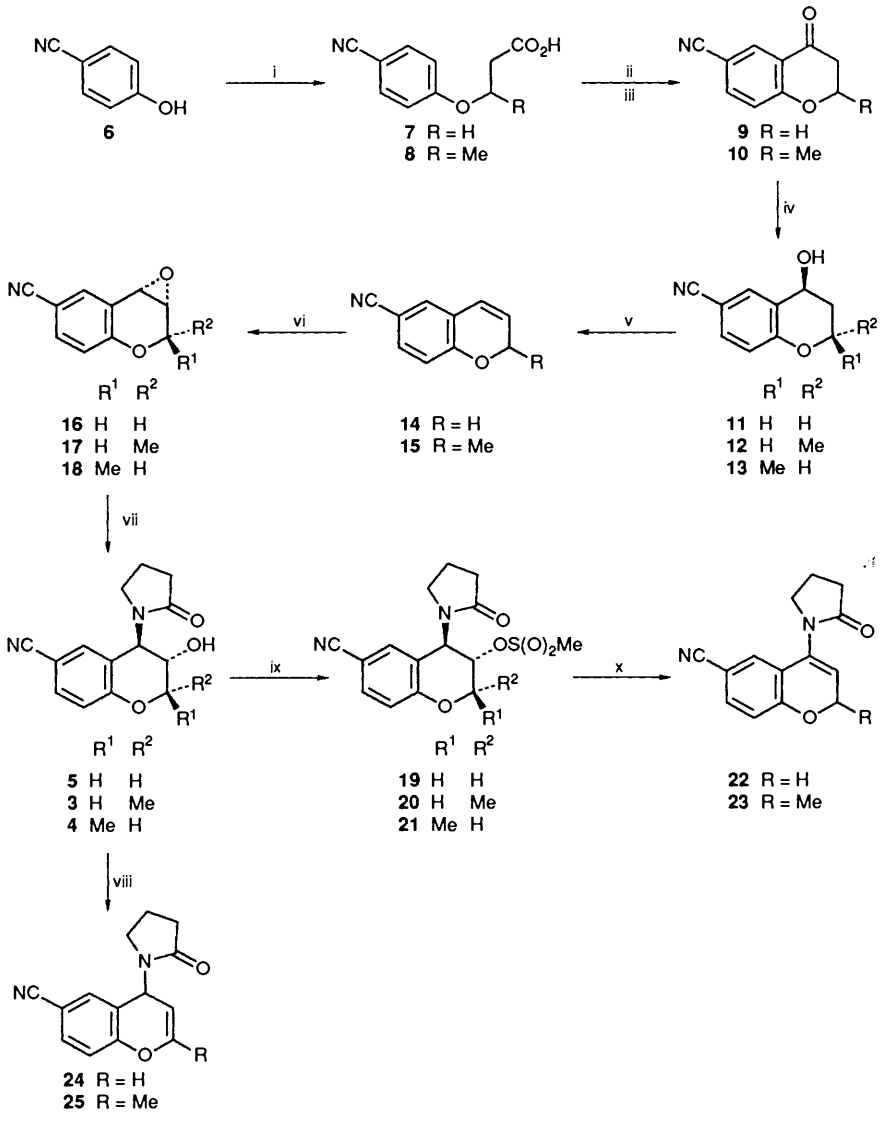
	R^1	R^2	R^3
1	CN	Me	Me
2	NO_2	Me	Me
3	CN	H	Me
4	CN	Me	H
5	CN	H	H

Results and Discussion

Benzopyrans and Dihydrobenzopyrans.—Whilst there are many methods available for the formation of 2,2-dimethylbenzopyrans, that involving condensation of an appropriate phenol with 3-chloro-3-methylbutyne followed by a thermally induced cyclisation of the resulting acetylenic ether is possibly the most versatile.[10] Since the cyclisation is facilitated by the presence of the geminal dialkyl group, however, the formation of C-2-unsubstituted benzopyrans using this route is less favourable.[11] Indeed, our attempts to use this method for the synthesis of benzopyrans such as **14** with powerful electron-withdrawing substituents has led invariably to the isolation of product in only poor yield.[12] The formation of these low yields is attributed to the exceptionally slow reaction rates in these instances, which results in complex side-reactions from which the isolation of pure material is difficult. As a consequence of this, we have chosen to prepare compound **14** by the procedure illustrated in Scheme 1. The alkylation of 4-cyanophenol **6** with β-propiololactone by a modification of the method of Gresham *et al.*[13] afforded a 93% yield of the propanoic acid **7**, which was quantitatively cyclised to the dihydrobenzopyranone **9** by ultrasonication of a solution of the anhydride in carbon disulphide with anhydrous aluminium chloride at ambient temperature. Alternative cyclisation procedures failed to give the high yields achievable in this two-stage reaction. The conversion of compound **9** into the corresponding benzopyran **14** was effected in a good overall yield by reduction to the alcohol **11** with potassium borohydride followed by dehydration with toluene-*p*-sulphonic acid (PTSA) in toluene at reflux.

Oxidation of the benzopyran **14** with *m*-chloroperbenzoic acid (MCPBA) subsequently afforded the epoxide **16** in 79% yield, which underwent smooth conversion into the amido alcohol **5** (50%) on treatment with potassium *t*-butoxide in pyrrolidin-2-one. The product derived from the dehydration of the amido alcohol **5** was largely dependent on the conditions under which the reaction was carried out; the reaction could be directed to give the non-conjugated alkene **24** or the conjugated isomer **22**. Hence, treatment of compound **5** with sodium hydride in tetrahydrofuran (THF) at reflux resulted in the isolation of the benzopyran **24** in 32% yield, whereas milder reaction conditions, involving prior conversion of the alcohol **5**

† Only relative stereochemistry shown throughout.



Scheme 1 *Reagents and conditions:* i, β-propiololactone or β-butyrolactone, KOBu^t, THF; ii, $(COCl)_2$, CH_2Cl_2, DMF, room temp.; iii, $AlCl_3$, CS_2, CH_2Cl_2; iv, KBH_4, MeOH; v, PTSA, toluene, reflux; vi, MCPBA, CH_2Cl_2; vii, KOBu^t, pyrrolidin-2-one; viii, NaH, THF, reflux; ix, $MeSO_2Cl$, Et_3N, CH_2Cl_2; x, KOBu^t, THF, room temp.

into the methanesulphonate **19** (67%) followed by elimination with potassium *t*-butoxide in THF at room temperature, avoided double-bond migration and gave the conjugated benzopyran **22** in 23% yield.

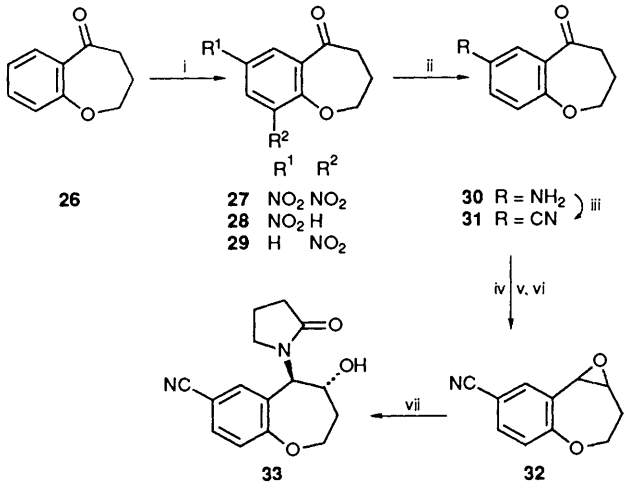
Although a C-2 monomethyl homologue of the dihydro-6-nitrobenzopyranol **2** has been prepared, and the biological activity shown to be reduced relative to that of compound **2** itself, the stereochemistry of this compound was not assigned.[9] It was considered to be important therefore to synthesize the two possible monomethyl isomers of cromakalim **1** in order to investigate the effects of selective removal of either the α or the β methyl group on biological activity. We have therefore synthesized and unambiguously characterised compounds **3** and **4** in order to establish whether just one isomer or both are substantially less potent than cromakalim **1**.

Both compounds may be conveniently prepared from the common intermediate isomeric epoxides **17** and **18** by following the same procedure as illustrated above for the dinor compound **16** (Scheme 1). The reaction of 4-cyanophenol with β-butyrolactone afforded the butanoic acid **8** (71%), which was cyclised *via* its anhydride to the dihydrobenzopyranone **10**. Reduction of compound **10** with potassium borohydride resulted in a quantitative yield of an enantiomeric mixture of the *trans* and *cis* alcohols **12** and **13** in an approximate ratio of 1:7, respectively. Dehydration of the mixed isomers in the presence of PTSA gave the corresponding alkene **15** in 50% yield, which generated a ~1:1 mixture of the two isomeric epoxides **17** and **18** in 67% yield on treatment with MCPBA. Comparison of the isomer ratio of products formed on oxidation of compound **15** with that found following the reduction of compound **10** highlights the unexpected preference exhibited in the reduction step. The amido alcohols **3** and **4** were subsequently prepared in 86% yield from this mixture of epoxides by reaction with potassium *t*-butoxide in pyrrolidin-2-one. Separation of the individual isomers using high performance liquid chromatography (HPLC) furnished the 2α,3α,4β-isomer **3** as the faster eluting material, followed by the 2β,3α,4β-isomer **4**.

As found with the di-nor compound **5**, the product derived from the dehydration of the mixed isomers **3** and **4** was governed by the conditions under which the reaction was carried out. Prior formation of the methanesulphonates **20** and **21**, which were generated in 89% yield on reaction of the mixture of alcohols **3** and **4** with methanesulphonyl chloride, followed by elimination with potassium *t*-butoxide at room temperature, afforded predominantly the conjugated product **23** (47%) together with an 18% yield of the isomeric alkene **25**. Separation

of these two compounds could be effected by chromatography. A better route to the non-conjugated isomer **25** involved heating the mixture of isomers **3** and **4** with sodium hydride in THF under reflux, when compound **25** was isolated in 69% yield as the sole product.

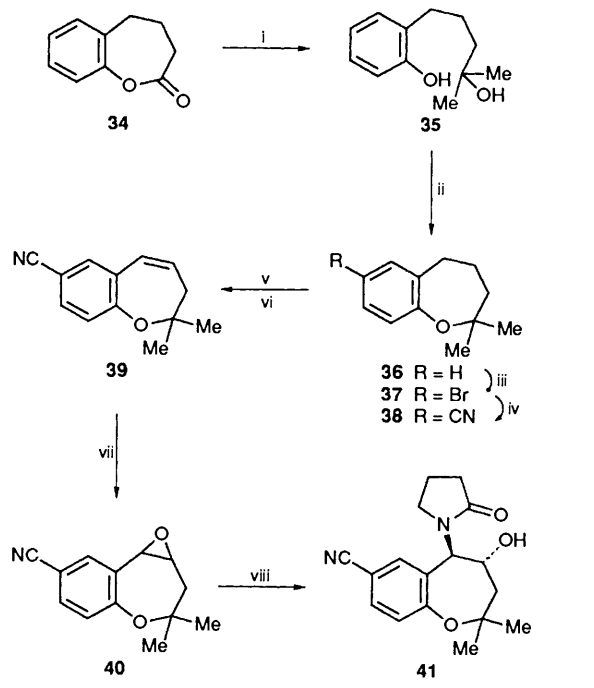
Benzoxepines.—Since no direct synthetic route to the 7-cyanobenzoxepine **33** is available, we chose to functionalise the parent ring system of the benzoxepine **26** (Scheme 2), which is



Scheme 2 *Reagents and conditions:* i, HNO_3 (see text and Experimental section); ii, H_2, 10% Pd/C, MeOH; iii, $NaNO_2$, HCl, EtOH followed by CuCN, KCN, water; iv, KBH_4, MeOH; v, PTSA, toluene, reflux; vi, MCPBA, CH_2Cl_2, room temp.; vii, KOBu^t, pyrrolidin-2-one, DMSO

available following a modification of the method of Tandon *et al.*[14] Attempts to improve on the earlier reported yields identified phosphoric oxide–Celite as the optimal reaction conditions for the cyclisation of 4-phenoxybutanoic acid and allowed the formation of compound **26** in 75% yield. Other conditions, however, such as phosphoric oxide in methanesulphonic acid, polyphosphoric acid ethyl ester, or sulphuric acid all failed to generate the ketone **26**, and conversion of 4-phenoxybutanoic acid into the acyl chloride followed by treatment with aluminium chloride resulted in only a 19% overall yield. The ketone **26** was highly sensitive to nitration and afforded the 7,9-dinitro derivative **27** in 75% yield on treatment with white fuming nitric acid at −50 °C. Under milder reaction conditions it was possible to limit nitration to the formation of mononitro derivatives, and a 6:1 mixture of the 7- and 9-nitro compounds, **28** and **29**, respectively, was formed in 93% yield. Conditions were not found for the formation of one or other mono nitro derivative exclusively, but pure isomers were isolable by chromatography. In general, however, it was found to be advantageous to convert the mixed nitro compounds into the corresponding amino derivatives, from which the desired 7-amino isomer **30** was readily isolated. This amine was subsequently converted into the cyanobenzoxepinone **31** in 73% yield by a Sandmeyer reaction. Reduction of compound **31** with potassium borohydride followed by dehydration and oxidation with MCPBA then furnished the epoxide **32** in good overall yield. Treatment of epoxide **32** with potassium *t*-butoxide in pyrrolidin-2-one resulted in the formation of the amido alcohol **33** in 43% yield. Limited attempts to convert compound **33** into the corresponding alkene *via* mesylation and elimination were unsuccessful, the reactions forming a multicomponent mixture.

The 2,2-dimethylbenzoxepine **41**, the ring-expanded analogue of cromakalim **1**, was prepared by an alternative to the above procedure starting from 1-tetralone (1-oxo-1,2,3,4-tetrahydronaphthalene) (Scheme 3). Baeyer–Villiger oxidation of 1-tetralone[15] gave the benzoxepinone **34** (84% yield), which afforded the hydroxy phenol **35** (96%) on reaction with methylmagnesium iodide. Compound **35** readily underwent dehydration when heated under reflux with PTSA in toluene to yield the benzoxepine **36** in 91% yield. Although attempts to nitrate compound **36** either directly or after conversion into the 5-keto derivative (formed by oxidation with potassium persulphate) were unsatisfactory, halogenation with bromine in buffered acetic acid resulted in a 37% yield of the 7-bromo derivative **37**. Reaction of compound **37** with copper(I) cyanide resulted in a smooth displacement of the halogen to give a 64% yield of the nitrile **38**, which on treatment with *N*-bromosuccinimide (NBS) and dehydrohalogenation afforded the alkene **39**. Oxidation of compound **39** with MCPBA then gave the epoxide **40** in 74% yield. In contrast to the di-nor epoxide **32**, compound **40** reacted poorly with pyrrolidin-2-one anion and gave the required amido alcohol **41** in only 9% yield.



Scheme 3 *Reagents and conditions:* i, MeMgI, Et_2O; ii, PTSA, toluene, reflux; iii, Br_2, $MeCO_2H$, $MeCO_2Na$, iv, CuCN, DMF, reflux; v, NBS, CCl_4; vi, DBN, THF, room temp.; vii, MCPBA, CH_2Cl_2; viii, KOBu^t, pyrrolidin-2-one

Structural Assignment of the Monomethyldihydrobenzopyranols **3** *and* **4**.—The structure of the dihydrobenzopyranols **3** and **4** has been unequivocally assigned by analysis of their high-field ^{1}H NMR spectra (see Table 1). In compound **4**, the coupling-constant-values of $^3J_{H2,H3}$ = 9.5 Hz and $^3J_{H3,H4}$ = 9.9 Hz indicated that the 2-H, 3-H and 4-H protons were all pseudoaxial relative to the benzopyran ring.[16–19] Furthermore, the observation of a mutual NOE between 2-H and 4-H confirmed their approximate *syn*-1,3-diaxial relationship. From this evidence it was concluded that compound **4** has the *trans*-C-2,C-3 and *trans*-C-3,C-4 stereochemistry and exists predominantly in the conformation having the dihydropyran substructure in a half-chair with the C-2, C-3 and C-4 substituents pseudoequatorial (Fig. 1). Although this conformation is expected to predominate, the existence of slight ring distortions or equilibria with minor conformations cannot be precluded, due to the submaximal values of the vicinal coupling constants in the above analysis.[16–19]

Table 1 ^{1}H NMR data for the amido alcohols **3** and **4**

	3			**4**		
Atom	δ_H [a]	^nJ-Values/Hz	NOEs observed	δ_H [a]	^nJ-Values/Hz	NOEs observed
2-H	4.36	$^3J_{2,2\text{-Me}}$ 6.6 $^3J_{2,3}$ 2.6 [b]	2-Me, 3-H, 5′-H$_a$	4.22	$^3J_{2,2\text{ Me}}$ 6.3 $^3J_{2,3}$ 9.5	4-H
2-Me	1.30	$^3J_{2,2\text{-Me}}$ 6.6	2-H, 3-H, 3-OH, 4-H	1.42	$^3J_{2,2\text{ Me}}$ 6.3	
3-H	3.89		2-H, 2-Me, 3-OH, 4-H, 5′-H$_a$	3.62		
3-OH	5.61	$^3J_{3,3\text{-OH}}$ 2.8		5.64	$^3J_{3,3\text{ OH}}$ 4.4	
4-H	4.99	$^3J_{3,4}$ 6.1 [b]	2-Me, 3-H, 3-OH, 5-H	5.06	$^3J_{3,4}$ 9.9	2-H
5-H	7.52			7.32		
7-H	7.63			7.61		
8-H	6.98			6.96		
3′-H	2.23–2.44			2.31–2.44		
4′-H	1.91			1.99		
5′-H$_a$	3.21			3.32		
5′-H$_b$	2.91			2.97		

[a] Solvent: $(CD_3)_2SO$, δ_H relative to δ_{TMS} 0 ppm. [b] In $(CD_3)_2SO$ at 120 °C; $^3J_{3,4}$ 5.8 Hz; $^3J_{2,3}$ 3.0 Hz. In $CDCl_3$ at room temperature; $^3J_{3,4}$ 6.3 Hz; $^3J_{2,3}$ 3.2 Hz.

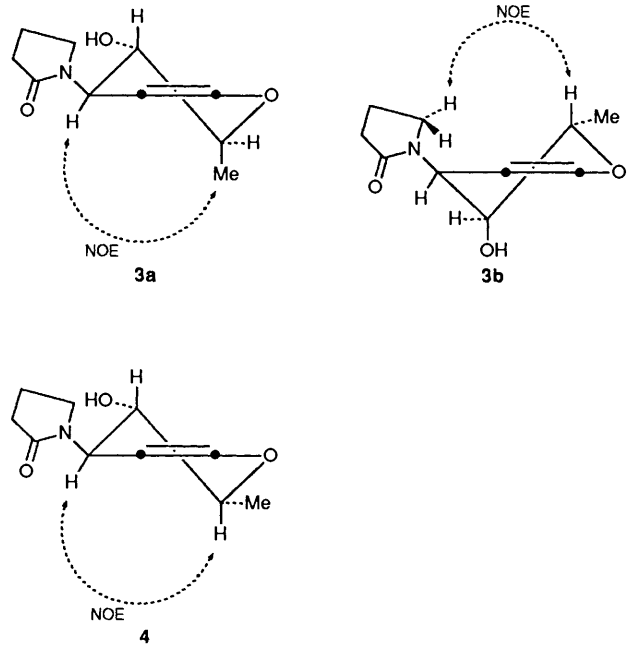


Fig. 1 Conformations of compounds **3** and **4**

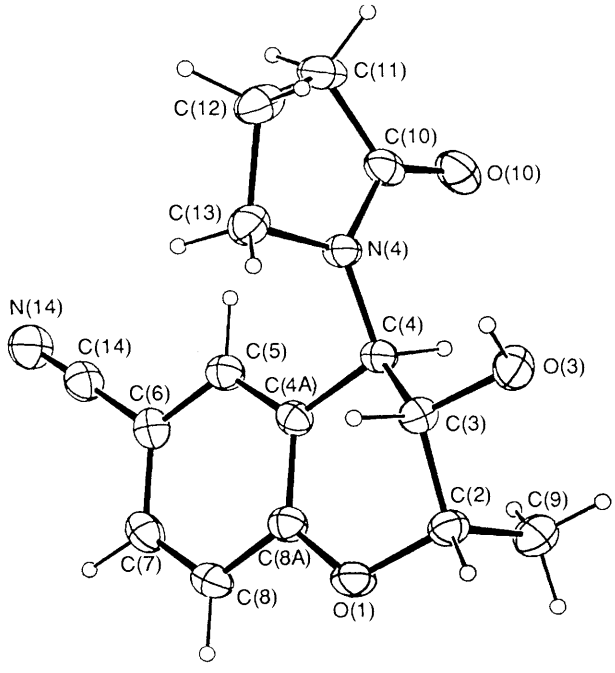


Fig. 2 X-Ray molecular structure of compound **3**

In compound **3**, the mutual NOE observed between 4-H and 2-Me was evidence of their *syn*-1,3-relationship and indicated that, for a dihydropyran half-chair substructural conformation, 4-H is orientated pseudoaxially to the ring whereas 2-H is orientated pseudoequatorially. It therefore followed that the vicinal coupling-constant-values of $^3J_{H2,H3}$ = 2.6 Hz and $^3J_{H3,H4}$ = 6.1 Hz, implied that the 3-H proton was orientated pseudoequatorially, *i.e.* the C-3, C-4 substituents were *cis*.[16–19] From the synthesis, however, it is evident that the C-3 hydroxy group and the C-4 amido moiety must be orientated *trans* relative to each other, since compound **3** is the product of ring cleavage of a *cis*-epoxide. It was therefore concluded that since 4-H and the 2-Me are *syn*-related and that the C-3, C-4 substituents are necessarily *trans*, then compound **3** has *cis*-C-2, C-3 stereochemistry (Fig. 1). Single-crystal X-ray analysis of compound **3** confirmed the relative stereochemistry of the pyran substituents (Fig. 2; see Table 2 for atomic co-ordinates). The data also show that compound **3** adopts a distorted half-chair conformation in the solid state with the C-2 methyl group occupying a pseudoaxial position. Furthermore, the C-4 substituent adopts an orthogonal orientation relative to the pyran ring with the carbonyl group pointing in the direction of the C-4 hydrogen atom. A similar conformation has been demonstrated for the 2,2-dimethyl homologue, cromakalim **1**, in both the solid state[20] and as the preferred conformation in solution.[20,21]

In solution the half-chair conformation resembling that found in the solid state (*i.e.*, **3a**, Fig. 1: dihedral angles; 2-H–C-2–C-3–3-H −57°, 3-H–C-3–C-4–4-H 175°) would not be consistent with the experimentally observed vicinal coupling constants, particularly those between the 3-H and the 4-H protons. For protons as depicted in sub-structure **3a**, the observed value of $^3J_{H3,H4}$ is clearly submaximal with respect to both the literature data[16–19] and those observed for compound **4**. The solution-state behaviour could be explained in two ways: namely that either a dynamic equilibrium involving at least two conformations is present or that compound **3** exists in a distorted half-chair conformation related to that observed in the solid state. The conformational equilibrium between substructure **3a** and some other conformer such as **3b** would adequately account for the measured vicinal coupling constants.

Table 2 Positional parameters and their estimated standard deviations for compound **3**

Atom	*x*	*y*	*z*
O(1)	0.446 6(1)	0.216 1(2)	0.596 62(7)
O(3)	0.081 8(1)	0.180 1(2)	0.612 23(8)
O(10)	0.078 8(1)	−0.095 8(2)	0.812 18(8)
N(4)	0.166 7(1)	0.152 7(2)	0.792 94(8)
N(14)	0.685 8(2)	0.062 5(2)	0.990 7(1)
C(2)	0.311 1(2)	0.170 8(2)	0.570 8(1)
C(3)	0.214 1(2)	0.211 2(2)	0.641 9(1)
C(4)	0.250 0(2)	0.112 1(2)	0.720 9(1)
C(4A)	0.399 2(2)	0.130 3(2)	0,741 0(1)
C(5)	0.451 3(2)	0.097 8(2)	0.822 2(1)
C(6)	0.588 3(2)	0.117 1(2)	0.839 9(1)
C(7)	0.674 6(2)	0.168 5(2)	0.775 7(1)
C(8)	0.624 2(2)	0.198 9(2)	0.695 0(1)
C(8A)	0.487 3(2)	0.179 3(2)	0.677 7(1)
C(9)	0.309 2(2)	−0.001 55(2)	0.542 6(1)
C(10)	0.090 4(2)	0.044 4(2)	0.833 4(1)
C(11)	0.026 7(2)	0.125 4(3)	0.908 6(1)
C(12)	0.042 5(2)	0.301 9(3)	0.890 3(1)
C(13)	0.164 9(2)	0.310 4(2)	0.833 1(1)
C(14)	0.640 6(2)	0.086 2(2)	0.924 5(1)

The existence of conformer **3b**, or some closely related structure, is also supported by the observation of an NOE at 5′-H upon irradiation of 2-H and by the NOE between the 2-Me and 3-H.

Biological Data.—The majority of the analogues described were of very low potency as relaxants of spontaneous tone in isolated guinea-pig trachealis, and all were significantly less potent than the parent compound cromakalim **1**.[6] It seems evident, therefore, that within the range of compounds investigated the dihydropyran ring of cromakalim is tolerant of little steric or conformational change. Whilst we have shown that ring contraction to the corresponding amidoindanols results in retention of biological activity,[5] there appears to be little scope for ring enlargement. Of interest, however, was the observation that whereas the *gem*-dimethyl group in the benzopyran series is essential for high potency,[9] its presence in the benzoxepine series was detrimental. Therefore, although the di-nor compound **33** was an effective, albeit relatively weak, relaxant of spontaneous tone in guinea-pig trachealis, the *gem*-dimethyl compound **41** was almost devoid of activity in this preparation.

Experimental

M.p.s were determined using a Büchi apparatus and are recorded uncorrected. IR spectra were measured as liquid films for oils or as dispersions in KBr or solutions for solids, using a Perkin-Elmer 197 spectrometer. NMR spectra were obtained with a Varian EM 360, Varian EM390, JEOL 270 GX or Bruker AM400 spectrometer with solutions in deuteriochloroform, unless otherwise noted, and referenced to tetramethylsilane as internal standard. *J*-Values are given in Hz. NOE difference spectra were performed using standard software on the JEOL or Bruker instruments. Mass spectral data were obtained from a VG-Micromass 70-70E instrument using electron-impact ionisation techniques. All organic extracts were dried over $MgSO_4$ and samples were chromatographed on silica gel except where stated.

3-(4′-*Cyanophenoxy*)*propanoic Acid* **7**.—Propiololactone (12.58 cm^3, 0.2 mol) was added dropwise to a solution of 4-hydroxybenzonitrile (23.8 g, 0.2 mol) and potassium *t*-butoxide (22.38 g, 0.2 mol) in THF (200 cm^3) under N_2 and the reaction mixture was stirred for 21 h. The solvent was evaporated off and the residue was taken up in water and extracted with ethyl aceate. The aq. phase was acidified with conc. HCl, extracted with ethyl acetate, and the combined organic layers were dried, filtered, and evaporated to give the title compound (28.53 g, 75%) as a solid, m.p. 139–141 °C (from benzene) (lit.,[22] 144–147 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3500, 3300–2600, 1750, 1720 and 1603; δ 2.92 (2 H, t, *J* 6, CH_2CO), 4.32 (2 H, t, *J* 6, OCH_2), 7.02 (2 H, d, *J* 8, 2′- and 6′-H), 7.68 (2 H, d, *J* 8, 3′- and 5′-H) and 8.9 (1 H, br, CO_2H) (Found: C, 61.7; H, 4.7; N, 7.15. Calc. for $C_{10}H_9NO_3$: C, 61.35; H, 4.9; N, 7.15%).

3-(4′-*Cyanophenoxy*)*butanoic acid* **8**, m.p. 91–92 °C, was similarly prepared in 71% yield by using β-butyrolactone; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3500, 3300–2600, 2235, 1750, 1720 and 1610; δ 1.4 (3 H, d, *J* 6, Me), 2.63 (1 H, dd, *J* 16, 5, CH*H*CO), 2.85 (1 H, dd, *J* 16, 7, C*H*HCO), 4.91 (1 H, m, OCH), 6.97 (2 H, d, *J* 8.8, 2′- and 6′-H), 7.59 (2 H, d, *J* 8.8, 3′- and 5′-H) and 9.25 (1 H, br, CO_2H) (Found: C, 62.95; H, 5.4; N, 6.45. $C_{11}H_{11}NO_3 \cdot 0.25H_2O$ requires C, 63.0; H, 5.5; N, 6.7%).

3,4-*Dihydro*-4-*oxo*-2H-1-*benzopyran*-6-*carbonitrile* **9**.—Oxalyl dichloride (7.07 cm^3, 82.11 mmol) was added slowly to a suspension of the acid **7** (7.85 g, 41.1 mmol) in dichloromethane (80 cm^3) at 0 °C. Dimethylformamide (DMF) (2 drops) was added and the reaction mixture was stirred at room temperature for 0.5 h. Evaporation of volatile materials gave a quantitative yield of the anhydride as a yellow oil, which was used without further purification; ν_{max}(film)/cm^{-1} 2220, 1790, 1600 and 1570.

To a solution of this material in carbon disulphide (150 cm^3) was added anhydrous aluminium chloride (18.16 g, 135.64 mmol) and the resulting solution was stirred under ultrasonication for 93.5 h. The solvent was evaporated off and the residue was treated with ice–HCl and extracted with ethyl acetate. The combined organic layers were washed with aq. sodium hydrogen carbonate, dried, filtered, and evaporated to give a brown solid, which was chromatographed. Elution with dichloromethane followed by ethyl acetate gave the *title compound* (3.8 g) as a pale yellow solid, m.p. 151–152 °C, in quantitative yield; ν_{max}(KBr)/cm^{-1} 2240, 1686, 1611 and 1568; δ 2.95 (2 H, t, *J* 6, CH_2CO), 4.67 (2 H, t, *J* 6, OCH_2), 7.1 (1 H, d, *J* 9, 8-H), 7.7 (1 H, dd, *J* 9, 2, 7-H) and 8.2 (1 H, d, *J* 2, 5-H) (Found: C, 69.25; H, 4.2; N, 8.0. $C_{10}H_7NO_2$ requires C, 69.35; H, 4.05; N, 8.1%).

3,4-*Dihydro*-2-*methyl*-4-*oxo*-2H-1-*benzopyran*-6-*carbonitrile* **10**, m.p. 179–180 °C (90%) was similarly prepared using the acid **8**; ν_{max}(KBr)/cm^{-1} 2235, 1700, 1625 and 1570; δ 1.57 (3 H, d, *J* 6, Me), 2.77 (2 H, m, 3-H_2), 4.7 (1 H, m, 2-H), 7.09 (1 H, d, *J* 8.5, 8-H), 7.7 (1 H, dd, *J* 8.5, 1.5, 7-H) and 8.2 (1 H, d, *J* 1.5 Hz, 5-H) (Found: C, 70.3; H, 4.9; N, 7.35. $C_{11}H_9NO_2$ requires C, 70.6; H, 4.85; N, 7.5%).

3,4-*Dihydro*-4-*hydroxy*-2H-1-*benzopyran*-6-*carbonitrile* **11**.—Potassium borohydride (1.3 g, 24.12 mmol) was added portionwise to a suspension of the ketone **9** (3.8 g, 21.96 mmol) in methanol (65 cm^3) at 0 °C. The reaction mixture was then stirred for 0.5 h and allowed to attain room temperature. Hydrochloric acid (2 mol dm^{-3}) was added and the reaction mixture was extracted with ethyl acetate. The dried organic phase was concentrated and the residue was chromatographed (ethyl acetate) to give the *title compound* (3.32 g, 86%), m.p. 104–105 °C; ν_{max}(KBr)/cm^{-1} 3400, 2232, 1618 and 1575; δ 2.0–3.5 (3 H, m, 3-H + OH), 4.3–4.45 (2 H, m, 2-H_2), 4.82 (1 H, dd, *J* 4.5, 8.5, 4-H), 6.9 (1 H, d, *J* 8.8, 8-H), 7.47 (1 H, dd, *J* 8.5, 2, 7-H) and 7.67 (1 H, d, *J* 2, 5-H) (Found: C, 68.2; H, 5.2; N, 7.9. $C_{10}H_9NO_2$ requires C, 68.55; H, 5.2; N, 8.0%).

3,4-Dihydro-4-hydroxy-2-methyl-2*H*-1-benzopyran-6-carbonitriles **12** and **13** were similarly prepared in quantitative yield as a mixture of *cis*- and *trans*-isomers (7:1) by using

ketone **10**; ν_{max}(KBr)/cm^{-1} 3600–3100, 2221, 1615 and 1576; δ(*cis*-isomer) 1.55 (3 H, d, *J* 6.3, Me), 1.84 (1 H, ddd, *J* 11.4, 11.3, 13.0, 3-H), 2.39 (1 H, ddd, *J* 13.0, 6.2, 1.9, 3-H), 3.29 (1 H, d, *J* 7.9, OH), 4.44 (1 H, qdd, *J* 11.4, 6.3, 1.9, 2-H), 4.99 (1 H, ddd, *J* 7.9, 11.3, 6.2, 4-H), 6.92 (1 H, d, *J* 8.5, 8-H), 7.50 (1 H, dd, *J* 8.5, 2.2, 7-H) and 7.89 (1 H, d, *J* 2.2, 5-H); δ(*trans*-isomer) 2.2 (1 H, dt, *J* 12, 2, 3-H), 4.55 (1 H, m, 2-H), 4.86 (1 H, m, 4-H), 7.00 (1 H, d, *J* 8.5, 8-H), 7.55 (1 H, dd, *J* 8.5, 2, 7-H) and 7.73 (1 H, d, *J* 2, 5-H); Me, OH and one 3-H proton hidden under peaks of major isomer.

2H-1-*Benzopyran*-6-*carbonitrile* **14**.—A mixture of the alcohol **11** (3.3 g, 18.86 mmol) and PTSA (0.47 g, 2.48 mmol) was stirred and heated under reflux in toluene (320 cm^3) under N_2 for 3 h and was then cooled. The reaction mixture was dried, filtered, and evaporated and the residual oil was chromatographed (dichloromethane) to give the title compound as an oil (1.99 g, 67%) (lit.,[11] m.p. 48–50 °C), which was sufficiently pure to be used in the next step; ν_{max}(film)/cm^{-1} 2226, 1606 and 1575; δ 5.00 (2 H, m, 2-H_2), 5.85 (1 H, td, *J* 10, 3, 3-H), 6.43 (1 H, td, *J* 10, 2, 4-H), 6.83 (1 H, d, *J* 9, 8-H), 7.25 (1 H, d, *J* 2, 5-H) and 7.45 (1 H, dd, *J* 9, 2, 7-H).

2-Methyl-2*H*-1-benzopyran-6-carbonitrile **15**, m.p. 51–52 °C (lit.,[11] 55.5–56 °C), was similarly prepared in 50% yield from the alcohols **12** and **13**.

3,4-*Epoxy*-3,4-*dihydro*-2H-1-*benzopyran*-6-*carbonitrile* **16**.—A mixture of the benzopyran **14** (1.915 g, 12.2 mmol) and MCPBA (80%; 3.66 g, 16.96 mmol) was stirred in dichloromethane (250 cm^3) at room temperature for 20 h and then further MCPBA (0.366 g, 1.69 mmol) was added. After 2 h the reaction mixture was washed successively with 10% aq. sodium sulphite and saturated aq. sodium hydrogen carbonate. The organic phase was dried, filtered, evaporated, and the residue chromatographed. Elution with dichloromethane gave the *title compound* (1.664 g, 79%) as a solid, m.p. 102–103 °C; ν_{max}/cm^{-1} 2228, 1615, 1584 and 1254; δ 3.85 (1 H, d, *J* 4.5, 3-H), 3.92 (1 H, d, *J* 4.5, 4-H), 4.28 (1 H, d, *J* 13, 2-H), 4.64 (1 H, d, *J* 13, 2-H), 6.91 (1 H, d, *J* 8.5, 8-H), 7.54 (1 H, dd, *J* 8.5, 2, 7-H) and 7.68 (1 H, d, *J* 2, 5-H) (Found: C, 69.3; H, 4.1; N, 8.0. $C_{10}H_7NO_2$ requires C, 69.35; H, 4.05; N, 8.1%).

3,4-*Epoxy*-3,4-*dihydro*-2-*methyl*-2H-1-*benzopyran*-6-*carbonitriles* **17** and **18** were similarly prepared from the benzopyran **15** in 67% yield as a mixture of *cis*- and *trans*-isomers (1:1); ν_{max}(KBr)/cm^{-1} 2230, 1620 and 1585; δ(*cis*- and *trans*-isomers represented by *c* and *t*) 1.35 (3 H, d, *J* 7, Me *t*), 1.60 (3 H, d, *J* 6.5, Me *c*), 3.65 (1 H, d, *J* 4.4, 3-H *t*), 3.71 (1 H, d, *J* 4.4, 3-H *c*), 3.89 (1 H, d, *J* 4.4, 4-H *t*), 3.94 (1 H, d, *J* 4.4, 4-H *c*), 4.39 (1 H, q, *J* 6.6, 2-H *c*), 4.84 (1 H, q, *J* 7, 2-H *t*), 6.89 (1 H, d, *J* 8.5, 8-H *c* + *t*), 7.53 (1 H, dd, *J* 8.5, 2, 7-H *c* + *t*), 7.65 (1 H, d, *J* 2, 5-H *t*) and 7.68 (1 H, d, *J* 2, 5-H *c*) (Found: C, 70.25; H, 4.8; N, 7.4. $C_{11}H_9NO_2$ requires C, 70.6; H, 4.85; N, 7.5%).

trans-3,4-*Dihydro*-3-*hydroxy*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-6-*carbonitrile* **5**.—Potassium *t*-butoxide (0.170 g, 1.51 mmol) was added to a solution of the epoxide **16** (0.261 g, 1.51 mmol) in pyrrolidin-2-one (3.5 cm^3) under N_2 and the mixture was stirred at room temperature for 4 h. Water was added and the solution was extracted with ethyl acetate. The combined extracts were dried, filtered, and evaporated to give an oil, which was chromatographed. Gradient elution from dichloromethane to ethyl acetate gave the *title compound* (0.150 g, 50%) as a solid, m.p. 216–217 °C; ν_{max}(KBr)/cm^{-1} 3420, 2225, 1671, 1612 and 1576; δ 2.15 (2 H, m, CH_2CH$_2$N), 2.58 (2 H, td, *J* 8, 1.5, CH_2CO), 3.12 (1 H, m, CH*H*N), 3.32 (1 H, m, C*H*HN), 3.41 (1 H, d, *J* 5, OH), 4.12 (2 H, m, 2- and 3-H), 4.40 (1 H, d, *J* 7, 2-H), 5.33 (1 H, d, *J* 8.5, 4-H), 6.95 (1 H, d, *J* 8.5, 8-H), 7.28 (1 H, d, *J* 2, 5-H) and 7.47 (1 H, dd, *J* 8.5, 2, 7-H) (Found: C, 64.95; H, 5.45; N, 10.8. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%).

3,4-*Dihydro*-3-*hydroxy*-2-*methyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-6-*carbonitriles* **3** and **4** were similarly prepared from the epoxides **17** and **18** in 86% yield as a mixture of the 2α,3α,4β- and 2β,3α,4β-isomer (45:55). The mixture (0.288 g) was separated by HPLC on a Spherisorb 55-ODS2 column. Elution wih methanol–water (1:1) at a flow rate of 9 cm^3 min^{-1} gave the 2α,3α,4β-isomer **3** (0.060 g), m.p. 199 °C; ν_{max}(KBr)/cm^{-1} 3600–3100, 2222, 1652, 1610 and 1572; δ[(CD_3)$_2$SO] 1.29 (3 H, d, *J* 6.5, Me), 1.91 (2 H, approx, quin., *J* 7.5, $CH_2CH_2CH_2$), 2.33 (2 H, m, CH_2CO), 2.91 (1 H, dd, *J* 9, 7, CH*H*N), 3.20 (1 H, dd, *J* 9, 7, C*H*HN), 3.89 (1 H, br s, 3-H), 4.36 (1 H, qd, *J* 6.3, 2.6, 2-H), 4.89 (1 H, d, *J* 6, 4-H), 5.60 (1 H, br s, OH), 6.90 (1 H, d, *J* 8.5, 8-H), 7.52 (1 H, d, *J* 2, 5-H) and 7.63 (1 H, dd, *J* 8.5, 2, 7-H) (Found: C, 66.3; H, 5.9; N, 10.35. $C_{15}H_{16}N_2O_3$ requires C, 66.15; H, 5.9; N, 10.3%) followed by the 2β,3α,4β-*isomer* **4** (0.080 g), m.p. 233 °C; ν_{max}(KBr)/cm^{-1} 3600–3050, 2225, 1658, 1611 and 1578; δ[(CD_3)$_2$SO] 1.42 (3 H, d, *J* 6.3, Me), 1.99 (2 H, approx. quin, *J* 7.4, $CH_2CH_2CH_2$), 2.37 (2 H, m, CH_2CO), 2.96 (1 H, m, CH*H*N), 3.3 (1 H, m, C*H*HN), 3.62 (1 H, dt, *J* 10, 4.4, 3-H), 4.23 (1 H, qd, *J* 9.3, 6, 2-H), 5.06 (1 H, d, *J* 10, 4-H), 5.63 (1 H, d, *J* 4.4, OH), 6.96 (1 H, d, *J* 8.5, 8-H), 7.33 (1 H, br s, 5-H) and 7.61 (1 H, dd, *J* 8.5, 2, 7-H) (Found: C, 66.35; H, 5.6; N, 10.35%).

trans-6-*Cyano*-3,4-*dihydro*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*yl Methanesulphonate* **19**.—A mixture of the benzopyranol **5** (0.116 g, 0.40 mmol), triethylamine (0.336 cm^3, 2.4 mmol) and methanesulphonyl chloride (0.186 cm^3, 2.4 mmol) was stirred at room temperature in dichloromethane (5 cm^3) for 15 h. Evaporation of the solvent gave an oil, which was chromatographed (ethyl acetate) to give the title compound (0.090 g, 67%) as an oil of sufficient purity for use in the next step; δ 2.1 (2 H, m, $CH_2CH_2CH_2$), 2.53 (2 H, m, CH_2CO), 3.2 (3 H, s, Me), 3.0–3.5 (2 H, m, CH_2N), 4.43 (2 H, ABX, *J* 12, 8, 4, 2-H_2), 5.15 (1 H, dt, *J* 7, 4, 3-H), 5.53 (1 H, d, *J* 7, 4-H), 7.04 (1 H, d, *J* 8, 8-H), 7.43 (1 H, d, *J* 2, 5-H) and 7.6 (1 H, dd, *J* 8, 2, 7-H).

6-Cyano-3,4-dihydro-2-methyl-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-yl Methanesulphonates **20** and **21** were similarly prepared (89%) from the benzopyranols **3** and **4** (7:3) as a mixture of 2α,3α,4β- and 2β,3α,4β-isomer (~4:1); δ(major isomer) 1.59 (3 H, d, *J* 6.3, Me), 2.1 (2 H, m, $CH_2CH_2CH_2$), 2.55 (2 H, m, CH_2CO), 2.97 (1 H, dt, *J* 8.2, 4.7, CH*H*N), 3.11 (3 H, s, Me), 3.39 (1 H, dt, *J* 8.2, 6.6, C*H*HN), 4.27 (1 H, dq, *J* 10, 6, 2-H), 4.78 (1 H, t, *J* 9.6, 3-H), 5.68 (1 H, d, *J* 9.6, 4-H), 6.97 (1 H, d, *J* 8.5, 8-H), 7.3 (1 H, d, *J* 2, 5-H), and 7.5 (1 H, dd, *J* 8.5, 2, 7-H).

4-(2-*Oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-6-*carbonitrile* **22**.—Potassium *t*-butoxide (0.032 g, 0.27 mmol) was added to a stirred solution of the mesylester **19** (0.090 g, 0.27 mmol) in THF (5 cm^3) at room temperature. After 20 min the reaction mixture was treated with 2 mol dm^{-3} HCl and extracted with ethyl acetate. The combined extracts were dried, filtered, and evaporated to give an oil, which was chromatographed (ethyl acetate) to give the *title compound* (0.015 g, 23%) as a solid, m.p. 169–171 °C; ν_{max}(KBr)/cm^{-1} 2225, 1687, 1663 and 1606; δ 2.3 (2 H, m, $CH_2CH_2CH_2$), 2.65 (2 H, m, CH_2CO), 3.64 (2 H, t, *J* 6, CH_2N), 5.08 (2 H, d, *J* 5, 2-H_2), 5.86 (1 H, t, *J* 5, 3-H), 6.9 (1 H, d, *J* 9, 8-H), 7.24 (1 H, d, *J* 2, 5-H) and 7.5 (1 H, dd, *J* 9, 2, 7-H) (Found: M$^+$, 240.0906. $C_{14}H_{12}N_2O_2$ requires M, 240.0897).

2-Methyl-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-6-carbonitrile **23**, m.p. 109 °C, was similarly prepared from the mixed mesylesters **20** and **21** in 47% yield; ν_{max}(KBr)/cm^{-1} 2225, 1689, 1659, 1607 and 1572; δ 1.52 (3 H, d, *J* 8.5, Me), 2.24

(2 H, m, $CH_2CH_2CH_2$), 2.59 (2 H, t, *J* 8.5, CH_2CO), 3.62 (2 H, m, CH_2N), 5.23 (1 H, dq, *J* 6.6, 3, 2-H), 5.72 (1 H, d, *J* 3, 3-H), 6.88 (1 H, d, *J* 8.2, 8-H), 7.2 (1 H, d, *J* 2, 5-H) and 7.43 (1 H, dd, *J* 8.2, 2, 7-H) (Found: M^+, 254.1049. $C_{15}H_{14}N_2O_2$ requires M, 254.1055), together with the C-2, C-3 double-bond isomer **25** (18%).

4-(2-*Oxopyrrolidin*-1-*yl*)-4H-1-*benzopyran*-6-*carbonitrile* **24**.—Sodium hydride (0.017 g of an 80% dispersion in mineral oil, 0.55 mmol) was added to a solution of the benzopyranol **5** (0.130 g, 0.50 mmol) in dry THF (5 cm^3) and the solution was heated under reflux for 16 h. The solvent was evaporated off and the residue was chromatographed (ethyl acetate) to give the *title compound* (0.038 g, 32%) as a solid, m.p. 122–123 °C; ν_{max}(KBr)/cm^{-1} 2227, 1685, 1671, 1611 and 1581; δ[$(CD_3)_2$SO] 1.87 (2 H, m, $CH_2CH_2CH_2$), 2.33 (2 H, m, CH_2CO), 2.77 (1 H, ddd, *J* 6, 8, 14, CH*H*N), 3.20 (1 H, ddd, *J* 6, 8, 14, C*H*HN), 5.09 (1 H, dd, *J* 6, 4, 3-H), 5.84 (1 H, d, *J* 4, 4-H), 7.08 (1 H, dd, *J* 6, 1.5, 2-H), 7.22 (1 H, d, *J* 8.5, 8-H), 7.57 (1 H, d, *J* 2, 5-H) and 7.77 (1 H, dd, *J* 8.5, 2, 7-H) (Found: C, 70.3; H, 5.2; N, 11.45. $C_{14}H_{12}N_2O_2$ requires C, 70.0; H, 5.05; N, 11.65%).

2-*Methyl*-4-(2-*oxopyrrolidin*-1-*yl*)-4H-1-*benzopyran*-6-*carbonitrile* **25**, m.p. 112 °C, was similarly prepared from the benzopyranols **3** and **4** in 69% yield; ν_{max}(KBr)/cm^{-1} 2221, 1698, 1672, 1622 and 1578; δ 1.95 (2 H, m, $CH_2CH_2CH_2$), 2.02 (3 H, s, Me), 2.47 (2 H, t, *J* 8.25, CH_2CO), 2.80 (1 H, m, CH*H*N), 3.28 (1 H, m, C*H*HN), 4.73 (1 H, dd, *J* 4.1, 1.1, 3-H), 6.00 (1 H, d, *J* 4, 4-H), 7.04 (1 H, d, *J* 8.5, 8-H), 7.51 (1 H, dd, *J* 8.5, 2.2, 7-H) and 7.56 (1 H, d, *J* 2.2, 5-H) (Found: M^+, 254.1058. $C_{15}H_{14}N_2O_2$ requires M, 254.1055).

3,4-*Dihydro*-7- *and* 9-*nitro*-1-*benzoxepine*-5(2H)-*one* **28** *and* **29**.—White fuming nitric acid (18 cm^3) was added to a stirred solution of the ketone **26** (2.15 g, 13.3 mmol)[14] in conc. nitric acid (20 cm^3) at −20 °C at a rate such that the temperature was maintained between −5 and −10 °C. The solution was stirred for 0.5 h at −10 °C, then poured into water (200 cm^3), and the resulting solid was collected by filtration, washed with water, and dried (*in vacuo*, phosphoric oxide) to give pure 7-*nitro isomer* **28** (2.13 g, 77%) as a yellow solid, m.p. 127–128 °C; δ 2.34 (2 H, quin, *J* 7, 3-H_2), 2.96 (2 H, t, *J* 7, 4-H_2), 4.38 (2 H, t, *J* 7, 2-H_2), 7.19 (1 H, d, *J* 9, 9-H), 8.26 (1 H, dd, *J* 9, 3, 8-H) and 8.63 (1 H, d, *J* 3, 6-H) (Found: C, 57.9; H, 4.5; N, 6.75. $C_{10}H_9NO_4$ requires C, 57.95; H, 4.4; N, 6.75%). The aq. residues were combined, then extracted with dichloromethane, and the extracts were dried and evaporated to give a yellow solid, which was chromatographed. Elution with chloroform–hexane (3:2) gave, first, a small quantity of mixed isomers (200 mg, 7%), which was followed by pure 9-*nitro isomer* **29** (256 mg, 9%) as a yellow solid, m.p. 56–58 °C; δ 2.28 (2 H, quin, *J* 7, 3-H_2), 2.96 (2 H, dd, *J* 7, 6.6, 4-H_2), 4.43 (2 H, t, *J* 6.6, 2-H_2), 7.24 (1 H, t, *J* 8, 7-H) and 7.92 (2 H, dd, *J* 1.8, 8, 6- and 8-H) (Found: C, 57.75; H, 4.35; N, 6.65%).

7- *and* 9-*Amino*-3,4-*dihydro*-1-*benzoxepine*-5(2H)-*one*.—To a solution of the above mixture of ketones **28** and **29** (5.1 g, 24.5 mmol; 3:1 ratio of 7- and 9-isomer) in methanol (200 cm^3) was added 10% palladium on carbon (0.5 g) and the mixture was hydrogenated. The mixture was filtered (Celite), the solvent was evaporated off and the residue was chromatographed. Elution with chloroform–diethyl ether (95:5) gave the 9-*amino isomer* (1.03 g, 23%) as a yellow oil, δ 2.2 (2 H, m, 3-H_2), 2.9 (2 H, m, 4-H_2), 4.0 (2 H, br s, NH_2), 4.25 (2 H, t, *J* 7, 2-H_2), 6.9 (2 H, m, 6- and 7-H) and 7.15 (1 H, dd, *J* 7, 2, 8-H) (Found: M^+, 177.0796. $C_{10}H_{11}NO_2$ requires M, 177.0790), followed by the 7-*isomer* **30** (3.36 g, 77%) as a brown oil, δ 2.15 (2 H, m, 3-H_2), 2.85 (2 H, m, 4-H_2), 3.55 (2 H, br s, NH_2), 4.2 (2 H, t, *J* 7, 2-H_2), 6.8 (1 H, dd, *J* 8, 3, 8-H), 6.9 (1 H, d, *J* 8, 9-H) and 7.05 (1 H, d, *J* 3, 6-H) (Found: M^+, 177.0796).

2,3,4,5-*Tetrahydro*-5-*oxo*-1-*benzoxepine*-7-*carbonitrile* **31**.—Aqueous sodium nitrite (1.26 g, 18.3 mmol in 20 cm^3) was added dropwise to a solution of the 7-aminobenzoxepine **30** (3.1 g, 17.5 mmol) in (1:2) aq. ethanol (60 cm^3) containing conc. HCl (4.4 cm^3) at 0 °C until an immediate reaction was observed with starch–iodide paper. The solution was stirred for 15 min and then added dropwise to a solution of copper(I) cyanide (14.8 g, 0.166 mol) and potassium cyanide (10.36 g, 0.159 mol) in water (50 cm^3) at 100 °C at such a rate that the temperature did not drop below 70 °C. The mixture was heated at 100 °C for a further 0.5 h, cooled, and extracted with ethyl acetate. The combined extracts were, dried, filtered, and evaporated to give a brown solid, which was chromatographed (dichloromethane) to give the *title compound* (2.39 g, 73%) as a cream solid, m.p. 82–83 °C; ν_{max}(Nujol)/cm^{-1} 2220, 1675 and 1600; δ 2.3 (2 H, m, 3-H_2), 2.9 (2 H, t, *J* 7, 4-H_2), 4.3 (2 H, t, *J* 6.3, 2-H_2), 7.15 (1 H, d, *J* 8.5, 9-H), 7.65 (1 H, dd, *J* 8.5, 2, 8-H) and 8.05 (1 H, d, *J* 2, 6-H) (Found: C, 70.35; H, 4.8; N, 7.45. $C_{11}H_9NO_2$ requires C, 70.55; H, 4.8; N, 7.5%).

4,5-*Epoxy*-2,3,4,5-*tetrahydro*-1-*benzoxepine*-7-*carbonitrile* **32**.—Reduction of the ketone **31** with potassium borohydride, as described above for the ketone **9**, gave 2,3,4,5-*tetrahydro*-5-*hydroxy*-1-*benzoxepine*-7-*carbonitrile* (78%), m.p. 83–84 °C (Found: 69.55; H, 5.8; N, 7.45. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.85; N, 7.4%), which was dehydrated with PTSA as previously described to give 2,3-*dihydro*-1-*benzoxepine*-7-*carbonitrile*, m.p. 71–72 °C (from diethyl ether–hexane) in quantitative yield (Found: C, 76.9; H, 5.05; N, 8.25. $C_{11}H_9NO$ requires C, 77.15; H, 5.3; N, 8.2%). Oxidation of this alkene as previously described then afforded the *title compound* (89%), m.p. 114–115 °C (from Et_2O); ν_{max}(Nujol)/cm^{-1} 2220 and 1600; δ 2.45 (1 H, br d, *J* 16, 3-H), 2.65 (1 H, m, 3-H), 3.7 (1 H, br s, 2-H), 3.8 (1 H, br d, *J* 4, 4-H), 4.1 (2 H, m, 2- and 5-H), 6.95 (1 H, d, *J* 8, 9-H), 7.5 (1 H, dd, *J* 8, 2, 8-H) and 7.75 (1 H, d, *J* 2, 6-H) (Found: C, 70.6; H, 4.9; N, 7.55. $C_{11}H_9NO_2$ requires C, 70.55; H, 4.85; N, 7.5%).

2-(4′-*Hydroxy*-4′-*methylpentyl*)*phenol* **35**.—To a stirred solution of methylmagnesium iodide (0.7 mol) in diethyl ether (150 cm^3) at 5 °C was added a solution of 4,5-dihydrobenzoxepine-2(3*H*)-one **34** (52.22 g, 0.32 mol)[15] in diethyl ether (200 cm^3) during 90 min. The mixture was stirred for 1 h at 15 °C and then poured into aq. ammonium chloride and extracted with dichloromethane. The combined organic layers were dried, filtered, and evaporated to give the *title compound* (59.9 g, 96%) as an off-white solid, m.p. 78–79 °C, which was used without further purification; ν_{max}(KBr)/cm^{-1} 3400 and 3100; δ 1.43 (6 H, s, Me), 1.72 (2 H, m, 3′-H_2), 1.91 (2 H, quin, *J* 7, 2′-H_2), 2.14 (1 H, br, OH), 2.85 (2 H, t, *J* 7.4, 1′-H_2), 6.79 (1 H, br, aromatic OH), 6.97–7.07 (2 H, m, ArH) and 7.23–7.31 (2 H, m, ArH) (Found: C, 74.15; H, 9.25. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.35%).

2,3,4,5-*Tetrahydro*-2,2-*dimethyl*-1-*benzoxepine* **36**.—A mixture of the phenol **35** (59.9 g, 0.31 mol) and PTSA (0.5 g) in toluene (300 cm^3) was heated under reflux with a Dean and Stark head for 18 h. The solvent was evaporated off and the residue was distilled under reduced pressure to give the *title compound* as an oil, b.p. 52 °C/0.15 mmHg; ν_{max}(film)/cm^{-1} 1485 and 1240; δ 1.24 (6 H, s, Me), 1.69 (2 H, m, 4-H_2), 1.80 (2 H, m, 3-H_2), 2.76 (2 H, t, 5.8, 5-H_2) and 6.88–7.12 (4 H, m, ArH) (Found: M^+, 176.1193. $C_{12}H_{16}O$ requires M, 176.1201).

7-*Bromo*-2,3,4,5-*tetrahydro*-2,2-*dimethyl*-1-*benzoxepine* **37**.—Bromine (18.2 g, 0.114 mol) was added to a stirred solution of the benzoxepine **36** (20 g, 0.114 mol) in acetic acid (150 cm^3) containing sodium acetate (47 g, 0.57 mol). The mixture was

stirred for 0.5 h, poured into water, and extracted with hexane. The combined organic layers were washed successively with water and aq. sodium hydroxide (2 mol dm^{-3}), dried, filtered and evaporated, and the residue was chromatographed. Elution with hexane–dichloromethane (1:1) gave the title compound (10.7 g, 37%) as an oil sufficiently pure for use in the next step; δ 1.25 (6 H, s, Me), 1.77 (4 H, m, 3- and 4-H_2), 2.70 (2 H, t, *J* 5.8, 5-H_2), 6.78 (1 H, d, *J* 9, 6-H) and 7.23 (2 H, m, 8- and 9-H).

2,3,4,5-*Tetrahydro*-2,2-*dimethyl*-1-*benzoxepine*-7-*carbonitrile* **38**.—A mixture of the benzoxepine **37** (10.7 g, 0.042 mmol) and copper(I) cyanide (4.8 g, 0.054 mol) was heated under reflux in DMF (200 cm^3) for 24 h. The mixture was poured into water and extracted with diethyl ether. The combined organic layers were washed successively with water and brine, dried, filtered, and evaporated, and the residue was chromatographed. Elution with hexane–dichloromethane (2:1) gave the title compound (6.3 g, 64%) as a solid, m.p. 42–43 °C, sufficiently pure for use in the next step; ν_{max}(film)/cm^{-1} 2220, 1600 and 1490; δ 1.28 (6 H, s, Me), 1.80 (4 H, m, 3- and 4-H_2), 2.78 (2 H, t, *J* 4.5, 5-H_2), 7.0 (1 H, d, *J* 9, 6-H) and 7.50 (2 H, m, 8- and 9-H).

2,3-*Dihydro*-2,2-*dimethyl*-1-*benzoxepine*-7-*carbonitrile* **39**.—A mixture of the benzoxepine **38** (1.05 g, 5.2 mmol) and NBS (0.98 g, 5.5 mmol) was heated under reflux in tetrachloromethane (15 cm^3) for 1 h, then cooled and filtered. The filtrate was evaporated and the residue was chromatographed. Elution with hexane–dichloromethane (3:1) gave 5-bromo-2,3,4,5-tetrahydro-2,2-dimethyl-1-benzoxepine-7-carbonitrile (1.1 g, 75%) as an oil, which was used without further purification. A mixture of this benzoxepine (1.95 g, 7 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1.3 cm^3, 10 mmol) was stirred in THF (25 cm^3) at room temperature for 42 h. Further DBN (0.5 cm^3) was added and the reaction mixture was heated under reflux for 8 h, then cooled and filtered. The filtrate was evaporated and the residue was chromatographed. Elution with diethyl ether–hexane (15:85) gave the *title compound* (0.78 g, 56%) as a pale yellow solid, m.p. 57–58 °C; ν_{max}(KBr)/cm^{-1} 2215, 1590, 1560, 1480 and 1250; δ 1.40 (6 H, s, Me), 2.58 (2 H, dd, *J* 5, 2.2, 3-H_2), 5.95 (1 H, dt, *J* 12, 5, 4-H), 6.36 (1 H, dt, *J* 12, 2, 5-H), 7.03 (1 H, d, *J* 9, 9-H) and 7.3–7.4 (2 H, m, 6- and 8-H) (Found: C, 78.3; H, 6.55; N, 6.95. $C_{13}H_{13}NO$ requires C, 78.35; H, 6.55; N, 7.05%).

4,5-*Epoxy*-2,3,4,5-*tetrahydro*-2,2-*dimethyl*-1-*benzoxepine*-7-*carbonitrile* **40**.—Oxidation of the dihydrobenzoxepine **39** with MCPBA as described above afforded the *title compound* (74%) as an oil; ν_{max}(film)/cm^{-1} 2220 and 1250; δ 1.30 (3 H, s, Me), 1.50 (3 H, s, Me), 1.65 (1 H, dd, *J* 15, 6, 3-H), 2.32 (1 H, dd, *J* 15, 5, 3-H), 3.50 (1 H, m, 4-H), 4.00 (1 H, d, *J* 4, 5-H), 7.00 (1 H, d, *J* 8, 9-H), 7.58 (1 H, dd, *J* 8, 2, 8-H) and 7.81 (1 H, d, *J* 2, 6-H) (Found: M^+, 215.0958. $C_{13}H_{13}NO_2$ requires M, 215.0946).

trans-2,3,4,5-*Tetrahydro*-4-*hydroxy*-5-(2-*oxopyrrolidin*-1-*yl*)-1-*benzoxepine*-7-*carbonitrile* **33**.—The *title compound*, m.p. 159–160 °C, was prepared (43%) from the epoxide **32** in a similar manner to the preparation of the benzopyranol **5** described above except that dimethyl sulphoxide (DMSO) was added as a cosolvent; ν_{max}(Nujol)/cm^{-1} 3330, 2220 and 1600; δ 2.1 (3 H, m, $CH_2CH_2CH_2$ + 3-H), 2.25 (1 H, m, 3-H), 2.55 (2 H, m, CH_2CO), 3.2 (1 H, m, CHN), 3.6 (1 H, m, CHN), 3.7 (1 H, br s, OH), 4.15 (1 H, m, 2-H), 4.4 (2 H, m, 2- and 4-H), 5.25 (1 H, d, *J* 8, 5-H), 7.1 (1 H, d, *J* 8, 9-H), 7.4 (1 H, d, *J* 2, 6-H) and 7.5 (1 H, dd, *J* 8, 2, 8-H) (Found: C, 66.05; H, 6.0; N, 10.3. $C_{15}H_{16}N_2O_3$ requires C, 66.15; H, 5.95; N, 10.3%).

trans-2,3,4,5-*Tetrahydro*-4-*hydroxy*-2,2-*dimethyl*-5-(2-*oxopyrrolidin*-1-*yl*)-1-*benzoxepine*-7-*carbonitrile* **41**, m.p. 161–162 °C, was similarly prepared (9%) from the epoxide **40** with pyrrolidin-2-one as solvent and chromatography of the final product on alumina (10% methanol–chloroform); ν_{max}(Nujol)/cm^{-1} 3230, 2220 and 1640; δ 1.17 (3 H, s, Me), 1.45 (3 H, s, Me), 1.8–2.10 (4 H, m, $CH_2CH_2CH_2$ + 3-H_2), 2.50 (2 H, m, CH_2CO), 2.90 (1 H, m, CHN), 3.45 (2 H, m, CHN + OH), 4.40 (1 H, dt, *J* 8, 3, 4-H), 5.25 (1 H, d, *J* 8, 5-H), 7.00 (1 H, d, *J* 9, 9-H) and 7.45–7.65 (2 H, m, 6- and 8-H) (Found: M^+, 300.1477. $C_{17}H_{20}N_2O_3$ requires M, 300.1473).

X-Ray Crystal Analysis of Compound **3**.—*Crystal data*. $C_{15}H_{16}N_2O_3$, M = 272.31. Monoclinic, a = 9.938(3), b = 8.411(3), c = 15.685(5) Å, β = 90.85(2)°, V = 1311 $Å^3$, space group $P2_1/c$ (14), Z = 4, D_c 1.38 g cm^{-3}, colourless, irregular prisms. Crystal dimensions 0.50 × 0.45 × 0.18 mm, μ(Mo-Kα) = 0.910 cm^{-1}.

Data collection and processing. CAD4 diffractometer, $\omega/2\theta$ mode, ω scan speed 2.50–6.70 deg min^{-1}, graphite-monochromated Mo-Kα radiation; 3330 reflections measured ($2° \leqslant 2\theta \leqslant 56°$, $0 \leqslant h \leqslant 13$, $0 \leqslant k \leqslant 11$, $-20 \leqslant l \leqslant 20$), 2987 unique, R = 0.040, giving 2326 with $I \geqslant 3\sigma(I)$. There were 230 variables including an extinction coefficient which refined to 5.94(1) × 10^{-7}.

Structure analysis and refinement. The structure of compound **3** was solved by direct methods using the SHELXS program series.[23] Atomic positions were initially refined with isotropic temperature factors and subsequently with anisotropic displacement parameters. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$. Weights, w, were assigned to the data as $w = 1/[\sigma(I_c) + 0.0016\ F_o^2]$. Final R- and R_w-values were 0.0442 and 0.0573. Positions for hydrogen atoms were located from difference Fourier maps and were allowed to refine. Isotropic temperature factors for hydrogens were held fixed at values calculated as 1.3 (B_{eq}) of the attached atom. The full-matrix least-squares refinement converged (max Δ/σ = 0.26) to values of the conventional crystallographic residuals listed above. A final difference Fourier map was featureless with maximum density of ±0.347 e $Å^{-3}$. Values of the neutral-atom scattering factors were taken from the International Tables for X-ray Crystallography. Atomic co-ordinates are found in Table 2.*

Note added in proof. A recent report published during the completion of this manuscript also describes the two isomeric monomethyl compounds **3** and **4**, and confirms the poor *in vitro* potency of these compounds as relaxants of smooth muscle tone.[24]

* *Supplementary data* (see section 5.6.3 of Instructions for Authors, issue 1). Bond lengths, angles, and thermal parameters have been desposited at the Cambridge Crystallographic Data Centre.

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