Structural Modifications of the Potassium Channel Activator Cromakalim: The C-3 Position

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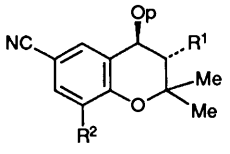
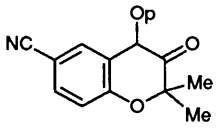
The syntheses of a selection of C-3 analogues of 6-cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-ol, the potassium channel activator cromakalim **1**, are described. Particular interest has focused on the corresponding 3-ketone **2** and compounds in which the hydroxy group of **1** has been replaced by fluorine, carbon and nitrogen containing residues. The hindered neopentylic nature of the C-3 hydroxy group in **1** has a marked effect on its reactivity and has necessitated the independent synthesis of many of these analogues from simpler precursors rather than from the direct modification of compound **1** itself.

Since the discovery of cromakalim, BRL 34915, **1** as a smooth muscle relaxant acting *via* a novel mechanism of action [1] and the rationalisation of its action in terms of the opening or activation of potassium channels in the cytosol of smooth muscle cells,[2] several workers have identified structurally distinct compounds



1 R^1 = OH, R^2 = H
6 R^1 = F, R^2 = H
8 R^1 = OH, R^2 = Cl



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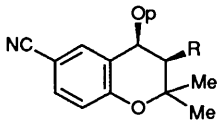


3 R = F
4 R = OH

Op = 2-oxopyrrolidin-1-yl throughout

that appear to exert their action through a similar mechanism.[3] Indeed, the potential that such compounds have in the treatment of a variety of disorders has attracted considerable interest.[4] Much of this interest has centred on the anti-hypertensive action of the potassium channel activators, but their potential in asthma is now being explored.[5]

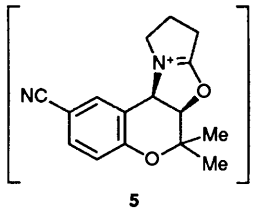
As part of our studies on the bronchodilator activity of cromakalim,[6] and more recently that of its active (3*S*,4*R*) enantiomer, BRL 38227, we have extensively studied the effects of structural modification in this series and particularly the effects of changes at the C-3 position.

In this paper we describe the synthesis of the 3-keto analogue of cromakalim and other structural variants which we expected would enhance our understanding of the features required for biological activity.

Results and Discussion

Whilst it is a simple matter to convert cromakalim **1** into ester [1] and ether [7] derivatives, conversion of the C-3 hydroxy into other functionalities is considerably less straightforward, usually involving the modification of precursors to cromakalim rather than functionalising the molecule itself. Typically, the problems which arise are highlighted by our attempts to replace the C-3 hydroxy by fluorine and to effect its oxidation to the ketone **2**.

The C-3 *Fluoride.*—Reaction of alcohol **1** with diethylaminosulphur trifluoride (DAST) gave not the expected 3-fluoro compound **3**, but a 37% yield of the *cis* alcohol **4**.[8] We speculate that compound **4** arises *via* intramolecular participation of the lactam moiety as shown in structure **5**, which is subsequently cleaved to compound **4** on hydrolytic work up. That this reaction does not take place purely because of the neopentylic nature of the C-3 hydroxy group has been



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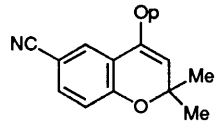

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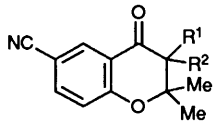


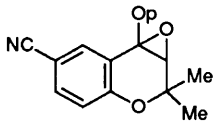
9 R^1 = R^2 = OH
10 R^1,R^2 = O
14 R^1 = H, R^2 = Br
47 R^1 = H, R^2 = NO_2
48 R^1 = R^2 = H

demonstrated by similar observations on dinor analogues of compound **1**.[9] It is interesting that treatment of the *cis* alcohol **4** with DAST afforded mainly the benzopyran **7** in 44% yield accompanied by trace amounts of the *trans* 3-fluoro derivative **6**. It is presumed that the *cis* amido alcohol **4** does not form an intermediate akin to **5** since this would involve the formation of a less favoured *trans* fused 5,6-ring system.[8] An analogous reaction on the thiolactam of compound **1** gave a complex mixture from which only a low yield of unchanged starting material was recovered.

The C-3 *Ketone.*—The neopentylic nature of the C-3 hydroxy group in compound **1** dominates much of its chemistry, and this

is particularly evident from reactions designed to effect direct oxidation at this position. Thus, cromakalim **1** resisted all attempts at direct oxidation to the ketone **2**. Many reagents including Jones and Swern oxidation[10] and chlorosulphonyl isocyanate–DMSO[11] all failed to produce compound **2**, or indeed to generate any identifiable product other than starting material. Since the 3-keto compound was of particular relevance with regard to defining the structural importance of the C-3 position, we have expended considerable effort in its synthesis. A number of other oxidants have been used in an attempt to oxidise cromakalim directly but none resulted in the isolation of ketone **2** in significant quantity. Thus, an excess of calcium hypochlorite in acetic acid[12] at 0 °C also failed to effect oxidation of the C-3 hydroxy group, but proved to be an effective method for the introduction of chlorine at C-8, furnishing compound **8** in 50% yield. Benzeneselenenic anhydride in tetrahydrofuran (THF) at reflux gave only the geminal diol **9**, in 87% yield on the basis of material consumed. It seems likely that compound **9** results from initial oxidation to the ketone **2** which subsequently undergoes α-selenenylation at C-4 followed by hydrolytic cleavage to the diketone **10**. Addition of water to compound **10** then results in the formation of the hydrate **9**. That this hydration occurs at the C-3 carbonyl group and not that at C-4 was evident from the ^{1}H NMR spectrum which shows little difference between the chemical shift of the C-5 proton (δ 8.3) in the hydrate from that (δ 8.4) in the diketone. Further support is derived from the coupled ^{13}C NMR spectrum (in [$^2H_6$]DMSO–D_2O) which shows 3-bond coupling of the C-4 ketone at δ 190.1 to 5-H and 4-bond coupling with 8-H. The same product **9** was also obtained when cromakalim **1** was treated with pyridine chlorochromate in dichloromethane at room temperature, although in this instance the yield was only 10% (43% on the basis of reclaimed starting material). A similar mechanism for the formation of the diol **9** to that suggested above can be postulated.

An attempt to oxidise the benzopyran **7** with *m*-chloroperbenzoic acid in dichloromethane at room temperature with the expectation that the desired intermediate epoxide **11** could be subsequently rearranged to ketone **2**, resulted only in low yields of the ring expanded benzodioxepinone **12**. We postulate that compound **2** is an intermediate in the reaction sequence



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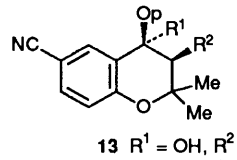
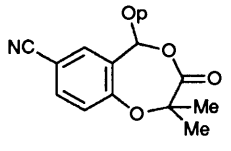


13 R^1 = OH, R^2 = Br
15 R^1 = Br, R^2 = OH



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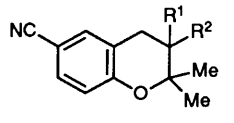
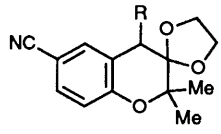
leading to compound **12** but it is unstable under the reaction conditions and undergoes a subsequent Baeyer–Villiger oxidation. This result contrasts with a recent finding by other workers[13] who found that with a 4-pyridone analogue of **7**, a more stable epoxide of type **11** was isolable and that this could be isomerised to the C-3 ketone. As an alternative route to the epoxide **11**, the benzopyran **7** was treated with aqueous *N*-bromosuccinimide (NBS) at ambient temperature over 45 min in an attempt to form the intermediate bromohydrin **13**. The only identified product, however, was the bromoketone **14** (isolated in 98% yield) arising from subsequent hydrolysis of compound **13**. The isomeric bromohydrin **15** is conceptually available by direct bromination of compound **1** but reaction with NBS in carbon tetrachloride afforded only unchanged starting material.

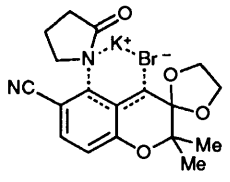
As a consequence of these difficulties we have attempted to prepare the ketone **2** using a different synthetic strategy. Initially we intended to halogenate the ketone **16**, which is readily available from 6-cyano-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran[1] on treatment with magnesium bromide–diethyl ether, but preliminary investigations revealed that the 4-halogeno derivatives of compound **16** were unstable and difficult to purify. Protection of the carbonyl moiety by ketalisation gave 88% of the dioxolane **17**, which formed the 4-



16 R^1, R^2 = O
17 R^1, R^2 = O[CH_2]$_2$O
28 R^1, R^2 = O[CH_2]$_3$O



18 R = Br
21 R = N_3
22 R = OH
23 R = OC(NH)Me
24 R = NH_2
25 R = N = PPh_3
26 R = NHCO[CH_2]$_3$Cl



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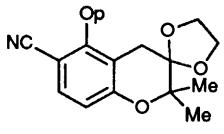

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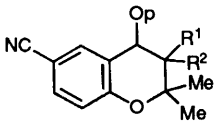
bromo derivative **18** in 50% yield on reaction with NBS in carbon tetrachloride. Compound **18** was accompanied by some 9% of the 4,4-dibromo derivative and 27% of unchanged ketal. The reaction of compound **18** with nucleophiles was of interest since the nature of the product varied with the nucleophile used.[14] In an endeavour to introduce the pyrrolidone moiety directly the bromo derivative **18** was treated with pyrrolidone anion at 100 °C during 4 h. Under these reaction conditions, the only product isolated was the C-5 substituted compound **19** which was obtained in 58% yield. Compound **19** presumably arises because of steric crowding at C-3 which effectively prevents entry of the bulky pyrrolidone anion at the C-4 position. Nevertheless, it is intriguing that no product arising from a similar S_N2' reaction at C-7 was detected under these conditions and it is possible that sole attack at C-5 is favoured by co-ordination of the potassium ion to the nitrogen nucleophile as illustrated in the intermediate **20**. Decomplexation experiments using 18-crown-6 support this contention.[14] If substitution at C-5 does indeed arise as a result of crowding by the ketal moiety, we expected that use of a smaller, linear anion such as azide would displace the halogen by a direct attack at C-4. This was verified and the 4-azido derivative **21** was isolated in 65% yield following reaction of the 4-bromo compound **18** with sodium azide in refluxing aqueous dioxane. To our surprise the anion of acetamide, which is relatively non-bulky, behaved differently from both pyrrolidone and azide by generating the 4-hydroxy derivative **22**. In this instance it is believed that the reaction proceeds *via* oxygen attack giving an intermediate acetamidate **23** which is subsequently cleaved on work-up. Intramolecular nucleophilic reactions at C-5 have been reported during the synthesis of large ring lactams akin to cromakalim, although the yields in this instance were not high.[15]

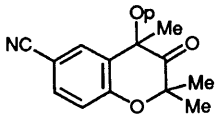
Fortunately, the azido derivative **21** proved to be a useful precursor even though its reduction to the amino compound **24** initially caused difficulties. Thus, catalytic transfer hydro-

genolysis in the presence of ammonium formate was unsuccessful and reaction of the azide **21** with triphenylphosphine gave a quantitative yield of the ylide **25** which resisted attempts at hydrolytic cleavage. Eventually, however, compound **21** was converted into the amino compound **24** in 93% yield using zinc and ammonium chloride in methanolic THF at room temperature. Acylation of the amine **24** with 4-chlorobutyryl chloride afforded 100% of the amide **26** which readily cyclised to the pyrrolidone **27** in 73% yield. Unfortunately, it proved exceptionally difficult to remove the ketal function from **27**. We presume that these difficulties occur because of the extreme crowding which exists at the C-3 quaternary neopentylic centre when it is flanked by a bulky C-4 substituent.

Since six-ring ketals are known to be more readily cleaved than their five-ring analogues[16] the ketone **16** was converted into the 1,3-dioxane **28** and the sequence described above was repeated. In this instance compound **28** was formed in 54% yield and was accompanied by 16% of the enol ether **29**. All other



27 R^1, R^2 = O $[CH_2]_2O$
30 R^1, R^2 = O $[CH_2]_3O$



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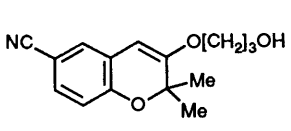

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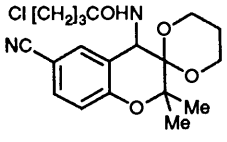

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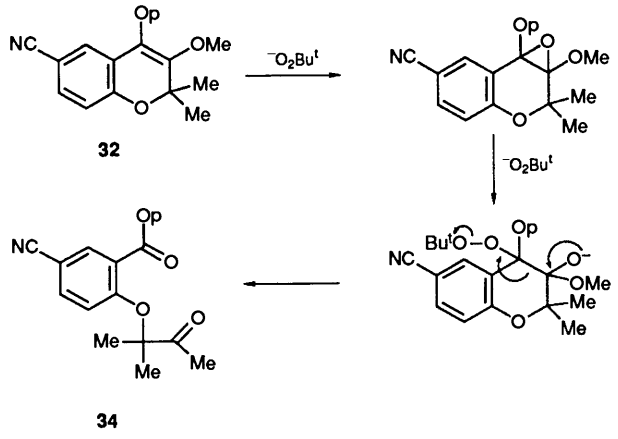
reactions leading to compound **30**, the dioxane homologue of compound **27**, proceeded as expected and in good yield. Once again, however, problems arose from attempted removal of the ketone protecting group, acidic or oxidative procedures for ketal deprotection resulting only in the recovery of starting material. Somewhat to our surprise hydrochloric acid at reflux did not hydrolyse the 1,3-dioxane moiety of compound **30** but resulted instead in cleavage of the pyrrolidone ring to give the chloro amide **31** in 38% yield. Replacing hydrochloric acid by the non-nucleophilic trifluoroacetic acid, however, overcame the problem of attack on the pyrrolidone and furnished the ketone **2** in 90% yield. From the spectroscopic data it is evident that the ketone **2** exists largely in the enolic form in polar solvents and, in consequence, embodies the dual structural characteristics of both cromakalim **1** and its anhydro derivative **7**, both of which are biologically active.

Methylation of the ketone **2** with methyl iodide and potassium t-butoxide in THF at 0 °C was interesting in that it afforded 31% of the expected enol ether **32** and 14% of the C-alkylated product **33** together with 3% of material believed to be the ring-opened product **34**. Compound **34** may arise as a result of peroxide contamination of the butoxide base following the sequence illustrated in Scheme 1.

Direct insertion of nitrogen at C-4 of the ketone **16** offers a potentially attractive route to the ketone **2** since this would provide a late precursor in the synthesis. Whereas an attempt to introduce nitrogen by an electophilic process using diphenylphosphinoylhydroxylamine[17] failed to effect insertion, reaction of the ketone **16** with tosyl azide resulted in a modest (20%) yield of the diazo compound **35** and the recovery of 34% of compound **16**. It was expected that the carbene derived from treatment of the diazo compound **35** with rhodium acetate

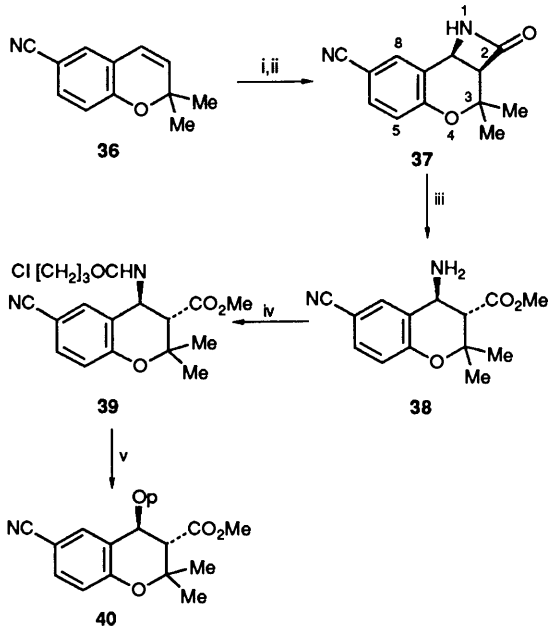


32 **34**

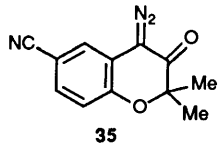
Scheme 1

would undergo insertion into the NH bond of pyrrolidone to give **2** directly, but under the conditions employed there was no evidence for formation of the required lactam.

Carbon Residues at C-3.—Since we were particularly interested in preparing analogues at C-3 in which the hydroxy group was replaced by carbon-containing residues, we next considered the synthesis of the ester **40** (Scheme 2). Reaction of the benzopyran **36**[1] with chlorosulphonyl isocyanate at room temperature for 21 d followed by reductive work-up gave 64% of the azetidinone **37**, which was readily ring opened and epimerised by subsequent methanolysis in the presence of sodium methoxide at room temperature to give the ester **38**. Condensation of compound **38** with 4-chlorobutyryl chloride at room temperature then furnished the amido ester **39** which readily cyclised to the required product **40** on treatment with a mixture of potassium carbonate and potassium iodide in acetone at reflux. The ester **40** was cleanly hydrolysed to the corresponding acid **41** on treatment with lithium iodide in collidine at 125 °C for 30 min. The conversion of compound **40** into the alcohol **42** was more problematic, care being needed to avoid concomitant nitrile reduction. The best conditions found



Scheme 2 *Reagents and conditions:* i, CSI, Na_2CO_3, 21 d, room temperature; ii, Na_2SO_3; iii, NaOMe, MeOH, room temperature; iv, $ClCO[CH_2]_3Cl$, NEt_3, CH_2Cl_2, room temperature; v, K_2CO_3, KI, Me_2CO, reflux, 24 h



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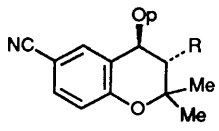
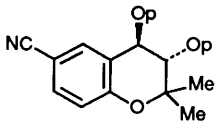


41 R = CO_2H
42 R = CH_2OH
43 R = CHO
44 R = CH_2OMe
45 R = CH_2F



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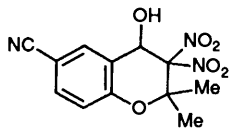

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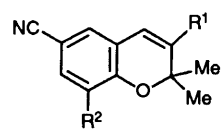
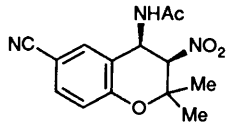


50 $R^1 = NO_2, R^2 = H$
51 $R^1 = H, R^2 = NO_2$



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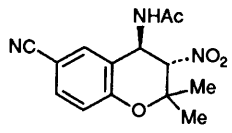

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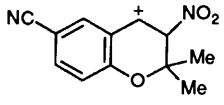

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involved treatment of the ester **40** with lithium borohydride in methanolic ether at reflux whereby compound **42** was isolated in 46% yield. Further manipulation of the alcohol **42** was straightforward. Thus, reaction with benzeneselenenic anhydride in THF at reflux afforded 83% of the aldehyde **43** and alkylation with methyl iodide in THF gave 86% of the ether **44**. Treatment of the alcohol **42** with DAST in dichloromethane at room temperature proceeded as expected to give the fluoromethyl derivative **45**, although the yield (30%) was relatively low.

Nitrogen Residues at C-3.—The direct insertion of nitrogen into the C-3 position of cromakalim **1** was found to be possible *via* an unusual reaction with pyrrolidone anion. Thus, on treatment with potassium t-butoxide and an excess of pyrrolidone at 100 °C for 5 h **1** was smoothly converted into an 84% yield of the diamide **46**, a compound which was first observed as a by-product in the large scale synthesis of cromakalim.[18] Since it appeared probable that compound **46** was formed by the prior dehydration to the benzopyran **7**, a similar reaction was carried out using this material as the substrate. In this instance, the reaction proceeded in 1 h at 100 °C and furnished compound **46** in 71% isolated yield. Whether this reaction is applicable to other nucleophiles is under investigation. A similar Michael addition on an analogous system has recently been reported by others.[13]

Attempts to effect the direct nitration of the benzopyran **7** at the 3-position by reaction with fuming nitric acid in acetonitrile at room temperature resulted only in the hydrolytic removal of the cyclic lactam moiety. The major products isolated were the 3-nitro compound **47** (34% yield) and unchanged compound **7** (38%) together with 3% of the chromanone **48**. A similar treatment of the benzopyran **36** was unsuccessful and resulted in no reaction. The reaction of compound **36** in ethyl acetate with nitronium iodide, prepared *in situ* from sodium nitrite and iodine,[19] provided 25% of the *gem*-dinitro compound **49** in addition to 73% of unchanged compound **36**. Formation of compound **49** may proceed *via* the required mono-nitro compound **50** by a further addition of reagent and subsequent hydrolysis. Alternatively, the intermediate nitroalkene **50** may undergo Michael addition by water followed by quenching with NO_2^+. Nitronium tetrafluoroborate in dichloromethane at room temperature failed to effect addition to benzopyran **36** and gave only low yields (7%) of the 8-nitro derivative **51**. The same reaction in acetonitrile, however, furnished 47% of a 1:1 mixture of the *cis* and *trans* 3-nitroacetamides **52** and **53**, respectively. It is evident that these two compounds are derived from addition of acetonitrile to the intermediate carbonium ion **54** followed by hydrolysis of the species thus formed.

Most of the modifications described here resulted in a marked reduction in biological activity when the compounds were assessed for their ability to relax spontaneous tone in guinea-pig isolated trachealis. The 3-keto compound **2**, on the other hand, showed similar potency to that of cromakalim itself.

Experimental

M.p.s were determined using a Büchi apparatus and are recorded uncorrected. IR spectra were measured as solutions in dichloromethane (for oils) or as dispersions in Nujol or KBr (for solids) using a Perkin-Elmer 197 spectrometer. NMR spectra were obtained with Varian EM360 (60 MHz), Em 390 (90 MHz), JEOL 270 GMX (270 MHz) or Bruker AM-400 (400 MHz) spectrometers with solutions in deuteriochloroform unless otherwise noted containing Me_4Si as standard. Mass spectral data were obtained from a VG-Micromass 70-70F instrument using electron impact ionisation techniques. All organic extracts were dried over $MgSO_4$ and samples were chromatographed on silica in all instances.

Reaction of Cromakalim with DAST.—DAST (1.5 ml, 11.38 mmol) was added to a stirred suspension of cromakalim **1** (1.76 g, 6.15 mmol) in dichloromethane (20 ml) and the resulting solution was stirred for 18 h at ambient temperature. The solvent was removed under reduced pressure and the residue chromatographed (ethyl acetate) to give *cis*-6-cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-ol **4** (0.65 g, 37%), m.p. 207–208 °C (lit.,[1] 216–217 °C).

Reaction of cis-6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*ol* **4** *with DAST.*—Reaction of the *cis* alcohol **4** (0.22 g, 0.77 mmol) with DAST (0.5 ml, 4.9 mmol) as described above afforded a dark oil (0.21 g) which was chromatographed (ethyl acetate) to give trans 6-*cyano*-3,4-*dihydro*-2,2-*dimethyl*-3-*fluoro*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **6** (8 mg, 4%), m.p. 180–190 °C; ν_{max}(KBr)/cm^{-1} 2235, 1693, 1618, 1580 and 1038; δ 1.35 (3 H, s, CH_3), 1.6 (3 H, s, CH_3), 2.15 (2 H, m, CH_2 CH_2CH_2), 2.6 (2 H, t, *J*/Hz: 7.8, CH_2CO), 3.1 (1 H, m, CH_2N), 3.4 (1 H, m, CH_2N), 4.55 (1 H, dd, *J*/Hz: 50 and 10, 3-H), 5.5 (1 H, dd, *J*/Hz: 16 and 10, 4-H), 6.9 (1 H, d, *J*/Hz: 8.5, 8-H), 7.45 (1 H, d, *J*/Hz: 2, 5-H) and 7.5 (1 H, dd, *J*/Hz: 8.5 and 2, 7-H) (Found: M^+, 289.1351. $C_{16}H_{17}FN_2O_2$ requires M, 289.1352).

Further elution afforded 6-cyano-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran **7** (90 mg, 44%), m.p. 142 °C (lit.,[1] 144–145 °C).

Attempted Direct Oxidation of **1**.—

(*a*) *Calcium hypochlorite.* A suspension of cromakalim **1** (0.500 g, 1.75 mmol) in acetonitrile–acetic acid [5 ml, (3:2)] was added dropwise during 10 min to a stirred solution of calcium hypochlorite (170 mg, 1.17 mmol) in water (4 ml) at 0 °C. Further hypochlorite was added until TLC showed the absence of compound **1** and the mixture was diluted with water. The solution was extracted with dichloromethane and the organic phase washed with aqueous $NaHCO_3$ and dried. Evaporation afforded a white solid which was chromatographed (ethyl acetate) to yield trans-8-*chloro*-6-*cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*ol* **8** (0.249 g, 50%), m.p. 268–270 °C; ν_{max}(KBr)/cm^{-1} 2236, 1672, 1602 and 1565; δ 1.3 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 2.12 (2 H, m, $CH_2CH_2CH_2$), 2.57 (2 H, dt, *J*/Hz: 8 and 2, CH_2CO), 3.00 (1 H, dt, *J*/Hz: 8.5 and 5 CH_2N), 3.39 (1 H, dd, *J*/Hz: 7.8 and 16, CH_2N), 3.77 (1 H, d, *J*/Hz: 10.5, 3-H), 5.24 (1 H, d, *J*/Hz: 10.5, 4-H), 7.17 (1 H, d, *J*/Hz: 1, 5-H or 7-H) and 7.54 (1 H, d, *J*/Hz: 1, 7-H or 5-H) (Found: C, 59.6; H, 5.3; N, 8.45. $C_{16}H_{17}Cl\ N_2O_3$ requires C, 59.9; H, 5.35; N, 8.75%).

(*b*) *Benzeneseleninic anhydride.* Benzeneseleninic anhydride (1.52 g, 4.22 mmol) was added to a solution of cromakalim **1** (550 mg, 1.92 mmol) in dry THF (45 ml) containing 4 Å molecular sieves and the solution was heated under reflux for 22 h. The reaction mixture was cooled, filtered and evaporated and the residual solid was chromatographed [ethyl acetate–hexane (1:1)] to give 6-*cyano*-2,2-*dimethyl*-4-*oxo*-2H-1-*benzopyran*-3,3-*diol* **9** (300 mg, 87% on the basis of recovered starting material), ν_{max}(KBr)/cm^{-1} 3460, 3380, 2240, 1707 and 1615; δ($CDCl_3$–D_2O) 1.44 (6 H, s, 2 × CH_3), 7.05 (1 H, d, *J*/Hz: 9, 8-H), 7.58 (1 H, dd, *J*/Hz: 9 and 2, 7-H) and 8.3 (1 H, d, *J*/Hz: 2, 5-H). Elemental analysis and melting points were inconsistent due to varying levels of hydration. Mass spectral analysis gave only the 3,4-diketone as a molecular ion (Found: M^+, 215.0589; $C_{12}H_9NO_3$ requires M, 215.0582).

Further elution afforded unchanged cromakalim **1** (103 mg).

(*c*) *Pyridinium chlorochromate.* Oxidation of cromakalim **1** (572 mg, 2 mmol) with pyridinium chlorochromate (862 mg, 4 mmol) in dichloromethane (20 ml) at room temperature during 64 h furnished the ketone **9** (43 mg) and unchanged compound **1** (440 mg).

Oxidation of Benzopyran **7** *with* m-*Chloroperbenzoic Acid.*—*m*-Chloroperbenzoic acid (431 mg, 2 mmol of 80% material) was added in one portion to a solution of compound **7** (536 mg, 2 mmol) in 1,2-dichloroethane (10 ml) and the resulting solution was stirred for 20 h at room temperature. After being washed with 10% aqueous sodium sulphite and aqueous $NaHCO_3$, the organic phase was dried and evaporated to give a colourless oil. Chromatography [ethyl acetate–hexane (7.3)] gave 7-*cyano*-2,2-*dimethyl*-5-(2-*oxopyrrolidin*-1-*yl*)-1,4-*benzodioxepin*-3-*one* **12** (88 mg, 35% based on recovered compound **7**) as an oil which was too unstable for analysis, ν_{max}(CH_2Cl_2)/cm^{-1} 2240, 1750, 1735, 1680 and 1610; δ 1.8 (6 H, s, 2 × CH_3), 1.9–2.8 (4 H, m, $COCH_2CH_2$), 3.95 (2 H, t, *J*/Hz: 6, CH_2N), 7.3 (1 H, d, *J*/Hz: 8, 9-H), 7.55 (1 H, d, *J*/Hz: 2, 6-H), 7.65 (1 H, dd, *J*/Hz: 8 and 2, 8-H) and 8.15 (1 H, s, 5-H).

Further elution afforded unchanged compound **7** (310 mg).

Reaction of the Benzopyran **7** *with Aqueous NBS.*—NBS (356 mg, 2 mmol) was added to a solution of compound **7** (268 mg, 1 mmol) in DMSO (2 ml) and water (0.044 ml). The reaction mixture was stirred for 45 min, poured into water and extracted with ethyl acetate. The combined extracts were washed with water, dried and evaporated to give an oil. Chromatography (ethyl acetate) of this gave 3-*bromo*-6-*cyano*-2,2-*dimethyl*-2H-1-*benzopyran*-4-*one* **14** (266 mg, 95%), m.p. 135 °C (ether–light petroleum); ν_{max}(CH_2Cl_2)/cm^{-1} 2220, 1705, 1615 and 1565; δ 1.57 (3 H, s, CH_3), 1.7 (3 H, s, CH_3), 4.4 (1 H, s, 3-H), 7.05 (1 H, d, *J*/Hz: 8, 8-H), 7.8 (1 H, dd, *J*/Hz: 8 and 2, 7-H) and 8.25 (1 H, d, *J*/Hz: 2, 5-H) (Found: C, 51.65; H, 3.65; N, 5.05. $C_{12}H_{10}BrNO_2$ requires C, 51.45; H, 3.6; N, 5.0%).

6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran*-3-*one* **16**.—A solution of 6-cyano-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran[1] (10.73 g, 53.38 mmol) in dry toluene (160 ml) was treated with magnesium bromide–diethyl ether (13.78 g, 53.38 mmol) at 80 °C for 2 h. The mixture was cooled, dilute HCl added and the product extracted into dichloromethane. The organic phase was dried, evaporated and the residual brown solid chromatographed (chloroform) to give the *title compound* **16** (6.15 g, 61%) as a white solid, m.p. 98–99 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 2220 and 1730; δ 1.5 (6 H, s, 2 × CH_3), 3.6 (2 H, s, 4-H), 7.05 (1 H, d, *J*/Hz: 8, 8-H), 7.4 (1 H, d, *J*/Hz: 2, 5-H), 7.55 (1 H, dd, *J*/Hz: 8 and 2, 7-H) (Found: C, 71.45; H, 5.5; N, 6.95. $C_{12}H_{11}NO_2$ requires C, 71.65; H, 5.5; N, 6.95%).

6-*Cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* **17**.—A mixture of ketone **16** (3.36 g, 16.7 mmol), ethane-1,2-diol (4.6 ml, 83.5 mmol) and toluene-*p*-sulphonic acid (317 mg, 1.67 mmol) in toluene (80 ml) was heated at reflux under a Dean–Stark head for 35 h until no further water distilled. The solution was cooled, extracted with dichloromethane and the organic phases were washed with aqueous $NaHCO_3$, dried and evaporated. Chromatography gave the *title compound* **17** (3.58 g, 87%) as a white solid, m.p. 84–85 °C; ν_{max}(KBr)/cm^{-1} 2225, 1612 and 1578; δ 1.35 (6 H, s, 2 × CH_3), 2.9 (2 H, s, 4-H), 4.05 (4 H, s, $[CH_2]_2$), 6.95 (1 H, d, *J*/Hz: 9, 8-H), 7.4 (1 H, d, *J*/Hz: 1.5, 5-H) and 7.45 (1 H, dd, *J*/Hz: 9 and 1.5, 7-H) (Found: C, 68.5; H, 6.1; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%).

4-*Bromo*-6-*cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* **18**.—A solution of benzopyran **17** (1.496 g, 6.1 mmol) in carbon tetrachloride (20 ml) was treated with NBS (0.993 g, 6.1 mmol) and azoisobutyronitrile (2 mg) and irradiated (tungsten lamp) while being stirred under reflux for 10 min. Further NBS (0.1 g, 0.61 mmol) was added and heating continued for an additional 5 min. After being cooled, the reaction mixture was filtered and evaporated. Chromatography of the residue [dichloromethane–hexane (9:1)] gave 4,4-*dibromo*-6-*cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* (221 mg, 9%), m.p. 182–183 °C; ν_{max}/cm^{-1} 2225 and 1609; δ 1.55 (6 H, s, 2 × CH_3), 4.2–4.8 (4 H, m, $[CH_2]_2$), 6.85 (1 H, d, *J*/Hz: 9, 8-H), 7.48 (1 H, dd, *J*/Hz: 9 and 2, 7-H) and 8.34 (1 H, d, *J*/Hz: 2, 5-H) (Found: C, 41.5; H, 3.1; N, 3.55. $C_{14}H_{13}Br_2NO_3$ requires C, 41.7; H, 3.25; N, 3.5%).

Further elution gave the *title compound* **18** (989 mg, 50%), m.p. 137–139 °C, ν_{max}/cm^{-1} 2230, 1610 and 1570; δ 1.35 (3 H, s, CH_3), 1.5 (3 H, s, CH_3), 4.0–4.55 (4 H, m, $[CH_2]_2$), 5.47 (1 H, s, 4-H), 6.9 (1 H, d, *J*/Hz: 8, 8-H), 7.5 (1 H, dd, *J*/Hz: 8 and 2, 7-H) and 7.9 (1 H, d, *J*/Hz: Me 2, 5-H) (Found: C, 51.75; H, 4.3; N, 4.4. $C_{14}H_{14}BrNO_3$ requires, C, 51.85; H, 4.35; N, 4.3%).

Finally unchanged ketal (400 mg, 27%) was eluted.

6-*Cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-*dimethyl*-5-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **19**.—To a stirred solution of potassium t-butoxide (95 mg, 0.85 mmol) in pyrrolidinone (1.6 ml) under N_2 was added a solution of the bromide **18** (276 mg, 0.85 mmol) in pyrrolidinone (2 ml). The mixture was stirred at 100 °C for 3.5 h before being cooled and diluted with water. Extraction with dichloromethane gave, after drying and evaporation, a yellow solid which was chromatographed (dichloromethane to ethyl acetate) to yield the *title compound* **19** (160 mg, 58%), m.p. 138–140 °C; ν_{max}(KBr)/cm^{-1} 2229, 1696, 1597 and 1577; δ 1.35 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 2.2–2.75

(4 H, m, $COCH_2CH_2$), 2.49 (1 H, d, *J*/Hz: 17, 4-H), 2.95 (1 H, d, *J*/Hz: 17, 4-H), 3.6 (1 H, m, CH_2N), 4.0–4.15 (5 H, m, $OCH_2CH_2O + CH_2N$), 6.91 (1 H, d, *J*/Hz: 8.5, 8-H) and 7.46(1 H, d, *J*/Hz: 8.5, 7-H) (Found: C, 64.85; H, 6.1; N, 8.25. $C_{18}H_{20}N_2O_4$ requires C, 65.85; H, 6.15; N, 8.55%).

6-*Cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2H-1-*benzopyran*-4-*ol* **22**.—Compound **18** (100 mg, 0.31 mmol) was added in one portion to a stirred solution of potassium t-butoxide (39 mg, 0.34 mmol) in acetamide (2.0 g, 33.8 mmol) at 80 °C under N_2 and the mixture was heated at 80 °C for 16 h. The mixture was cooled, diluted with water and extracted with ethyl acetate. The dried organic phase was concentrated and the residual oil was chromatographed [ethyl acetate–hexane (2:1)] to yield the *title compound* **22** (44 mg, 54%) as a white solid, m.p. 77–79 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 2210 and 1610; δ 1.34 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.45 (1 H, d, *J*/Hz: 10, OH), 4.12 (2 H, m, OCH_2), 4.27 (2 H, m, OCH_2), 4.77 (1 H, d, *J*/Hz: 10, 4-H), 6.85 (1 H, d, *J*/Hz: 8.5, 8-H), 7.45 (1 H, dd, *J*/Hz: 8.5 and 2, 7-H) and 7.8 (1 H, d, *J*/Hz: 2, 5-H) (Found: M^+, 261.1003. $C_{14}H_{15}NO_4$ requires M, 261.1001).

4-*Amino*-6-*cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* **24**.—Sodium azide (1.13 g, 17.4 mmol) was added to a solution of **18** (490 mg, 1.51 mmol) in aqueous dioxane (2:5, 7 ml) and the mixture was stirred under reflux for 25 h. The mixture was cooled, diluted with water and extracted with ethyl acetate. The dried extracts were evaporated and the residue chromatographed (dichloromethane) to yield 4-*azido*-6-*cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-dimethyl-2H-1-benzopyran **21** (280 mg, 65%), δ 1.4 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 4.12–4.48 (4 H, m, 2 × OCH_2), 4.6 (1 H, s, 4-H), 5.98 (1 H, d, *J*/Hz: 9, 8-H), 7.58 (1 H, dd, *J*/Hz: 9 and 2, 7-H) and 7.78 (1 H, d, *J*/Hz: 2, 5-H).

A mixture of compound **21** (180 mg, 0.64 mmol), zinc dust (167 mg, 2.56 mmol) and ammonium chloride (253 mg, 4.74 mmol) in methanolic THF (2:1; 3 ml) was stirred at room temperature for 19 h. It was then filtered (Celite) and partitioned between water and dichloromethane. The organic phase was separated, dried and concentrated to give the title compound **24** (154 mg, 93%) as an oil which was not purified further, δ 1.3 (3 H, s, CH_3), 1.4 (3 H, s, CH_3), 2.0 (2 H, m, NH_2), 4.0 (1 H, br s, 4-H), 4.2 (4 H, br s, 2 × OCH_2), 6.8 (1 H, d, *J*/Hz: 8, 8-H), 7.4 (1 H, dd, *J*/Hz: 8 and 2, 7-H) and 7.95 (1 H, d, *J*/Hz: 2, 5-H).

6-*Cyano*-3,3-*ethylenedioxy*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **27**.—A mixture of crude compound **24** (154 mg, 0.60 mmol), triethylamine (0.087 ml, 0.60 mmol) and 4-chlorobutyryl chloride (0.069 ml, 0.60 mmol) in dichloromethane (3 ml) was stirred at room temperature for 24 h. The reaction mixture was then diluted with water and the organic phase separated, dried and evaporated to give 4-(4-chlorobutyrylamido)-6-cyano-3,3-ethylenedioxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran **26** (220 mg, 100%) as a beige solid, δ 1.4 (6 H, br s, 2 × CH_3), 1.9–2.8 (4 H, m, $[CH_2]_2CO$), 3.65 (2 H, m, CH_2Cl), 4.15 (4 H, br s, 2 × OCH_2), 5.55 (1 H, d, *J*/Hz: 9, 4-H), 6.25 (1 H, d, *J*/Hz: 9, NH), 6.85 (1 H, d, *J*/Hz: 9, 8-H) and 7.4 (2 H, m, C-7, 5-H). Anhydrous K_2CO_3 (4.356 g, 26.28 mmol) was added to compound **26** (220 mg, 0.60 mmol) and potassium iodide (378 mg, 2.28 mmol) in dry acetone (50 ml) and the mixture was stirred at reflux for 68 h. The mixture was cooled, concentrated and partitioned between dichloromethane and water. The organic phase was separated, dried and evaporated and the residue was chromatographed (ethyl acetate) to give the *title compound* **27** (143 mg, 73%) as a white solid, m.p. 177 °C; $\nu_{max}(KBr)/cm^{-1}$ 2226, 1690, 1613 and 1576; δ1.45 (6 H, s, 2 × CH_3), 2.1 (2 H, m, $CH_2CH_2CH_2$), 2.5 (2 H, m, CH_2CO), 3.3 (2 H, m, CH_2N), 4.1 (4 H, m, 2 × OCH_2), 5.77 (1 H, s, 4-H), 7.0 (1 H, d, *J*/Hz: 8, 8-H), 7.25 (1 H, d, *J*/Hz: 2, 5-H), 7.55 (1 H, dd, *J*/Hz: 8 and 2, 7-H) (Found: C, 65.65; H, 6.25; N, 8.35. $C_{18}H_{20}N_2O_4$ requires C, 65.85; H, 6.15; N, 8.55%).

6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-3,3-*propylenedioxy*-2H-1-*benzopyran* **30**.—Reaction of compound **16** with propane-1,3-diol and carrying through the same sequence of reactions as those described above for compound **27** furnished the title compound **30** which was used without further purification, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2230 and 1675; δ 1.38 (3 H, s, CH_3) 1.47 (3 H, s, CH_3), 1.5 (2 H, m, $[OCH_2]_2CH_2$), 2.05 (2 H, m, $CH_2CH_2CH_2N$), 2.55 (2 H, m, CH_2CO), 3.15 (1 H, m, NCH_2), 3.55 (1 H, m, NCH_2), 3.8–4.3 (4 H, m, 2 × OCH_2), 5.78 (1 H, s, 4-H), 6.94 (1 H, d, *J*/Hz: 9, 8-H), 7.3 (1 H, d, *J*/Hz: 2, 5-H) and 7.5 (1 H, dd, *J*/Hz: 9 and 2, 7-H).

6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*one* **2**.—A mixture of compound **30** (0.992 g, 3.06 mmol) in trifluoroacetic acid (80 ml) and water (25 ml) was heated at 50 °C for 16 h and the cooled solution was concentrated. The residue was partitioned between dichloromethane and water and the organic layer was separated, dried and evaporated to give a pink solid. Chromatography (ethyl acetate) of this provided the *title compound* **2** (780 mg, 90%) as a white crystalline solid, m.p. 162–163 °C; $\nu_{max}(KBr)/cm^{-1}$ 2620, 2230, 1745 and 1700–1600; δ ($[^2H_6]DMSO$) (mainly the enol form) 1.45 (6 H, s, 2 × CH_3), 2.14 (2 H, m, $CH_2CH_2CH_2$), 2.38 (2 H, m, CH_2CO), 3.43 (2 H, t, *J*/Hz: 7, CH_2N), 6.89 (1 H, d, *J*/Hz: 8, 8-H), 7.10 (1 H, d, *J*/Hz: 2, 5-H), 7.41 (1 H, dd, *J*/Hz: 8 and 2, 7-H) and 10.18 (1 H, m, OH); δ ($CDCl_3$) (mainly the ketone form) 1.4 (3 H, s, CH_3), 1.6 (3 H, s, CH_3), 2.2 (2 H, m, $CH_2CH_2CH_2$), 2.6 (2 H, t, *J*/Hz: 8, CH_2CO), 3.18 (1 H, td, *J*/Hz: 5 and 9, CH_2N), 3.36 (1 H, td, *J*/Hz: 8 and 8, CH_2N), 5.92 (1 H, s, 4-H), 7.1 (1 H, d, *J*/Hz: 8, 8-H), 7.32 (1 H, d, *J*/Hz: 1.5, 5-H) and 7.59 (1 H, dd, *J*/Hz: 8 and 1.5, 7-H) (Found: M^+, 284.1155. $C_{16}H_{16}N_2O_3$ requires M, 284.1161).

Methylation of Compound **2**.—Potassium t-butoxide (44 mg, 0.387 mmol) was added to a stirred solution of the ketone **2** (100 mg, 0.352 mmol) and iodomethane (0.11 ml, 1.76 mmol) in THF at 0 °C. Additional iodomethane (0.11 ml) was added after 3.5 h and stirring was continued for 21 h at room temperature. After evaporation of the solvent, the residue was chromatographed (ethyl acetate) to give *methyl* α-*methyl*-[4-*cyano*-2-(2-*oxopyrrolidin*-1-*yl*)*carbonyl*]*phenoxypropionate* **34** (5 mg, 3%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$: 2225, 1745, 1675, 1605 and 1578; δ 1.60 (6 H, s, 2 × CH_3), 2.14 (2 H, quin., *J*/Hz: 7, $CH_2CH_2CH_2$), 2.58 (2 H, t, *J*/Hz: 8, CH_2CO), 3.74 (3 H, s, CO_2Me), 3.98 (2 H, t, *J*/Hz: 7.4, CH_2N), 6.69 (1 H, d, *J*/Hz: 8.8, 6-H), 7.56 (1 H, d, *J*/Hz: 2, 3-H), 7.59 (1 H, dd, *J*/Hz: 8.2 and 2, 5-H) (Found: M^+, 330.1197. $C_{17}H_{18}N_2O_3$ requires M, 330.1216). This was followed by 6-*cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-*methyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*one* **33** (15 mg, 14%), m.p. 58–60 °C, $\nu_{max}(KBr)/cm^{-1}$ 2230, 1740, 1690, 1610 and 1582; δ 1.46 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 1.66 (3 H, s, CH_3), 2.28 (2 H, m, $CH_2CH_2CH_2$), 2.47 (2 H, m, CH_2CO), 3.82 (2 H, m, CH_2N), 7.07 (1 H, d, *J*/Hz: 8, 8-H), 7.35 (1 H, d, *J*/Hz: 2, 5-H), 7.52 (1 H, dd, *J*/Hz: 8 and 2, 7-H) (Found: M^+, 298.1328. $C_{17}H_{18}N_2O_3$ requires M, 298.1317).

Finally 6-*cyano*-2,2-*dimethyl*-3-*methoxy*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **32** was eluted (33 mg, 31%), m.p. 131–132 °C; $\nu_{max}(KBr)/cm^{-1}$ 2224, 1695, 1646, 1601 and 1576; δ 1.52 (6 H, s, 2 × CH_3), 2.1–2.7 (4 H, m, $[CH_2]_2CO$), 3.55 (2 H, d, *J*/Hz: 6, CH_2N), 3.8 (3 H, s, OCH_3), 6.82 (1 H, d, *J*/Hz: 8, 8-H), 7.0 (1 H, d, *J*/Hz: 2, 5-H) and 7.35 (1 H, dd, *J*/Hz: 8 and 2, 7-H) (Found: M^+, 298.1331. $C_{17}H_{18}N_2O_3$ requires M, 298.1317).

7-*Cyano*-3,3-*dimethyl*-2a,8b-*dihydroazeto*[3,2-c]*benzopyran*-2(1H)-*one* **37**.—Chlorosulphonyl isocyanate (25 ml, 277.8

mmol) was added to a mixture of **36**[1] (9.25 g, 50 mmol) and sodium carbonate (0.50 g, 4.7 mmol) and the resulting brown solution was stirred under N_2 for 21 d. The reaction was carefully quenched with water and the mixture extracted with dichloromethane. The combined extracts were concentrated to 100 ml and a solution of sodium sulphite (20 g, 95 mmol) and dipotassium hydrogen phosphate (12 g, 70 mmol) in water (100 ml) added to them; the mixture was then stirred for 1.5 h. Separation of the phases and evaporation of the dried organic phase afforded a white solid which was chromatographed [ethyl acetate–light petroleum (3:1) to ethyl acetate] to give the *title compound* **37** (7.3 g, 64%), m.p. 190–191 °C; ν_{max}(Nujol)/cm^{-1} 3230, 2230, 1750, 1610, 1580, 1490 and 1460; δ 1.14 (3 H, s, CH_3), 1.73 (3 H, s, CH_3), 3.62 (1 H, d, *J*/Hz: 5.5, 2a-H), 4.68 (1 H, d, *J*/Hz: 5.5, 8b-H), 6.18 (1 H, m, NH), 7.00 (1 H, d, *J*/Hz: 8.25, 5-H), 7.54 (1 H, d, *J*/Hz: 2.2, 8-H) and 7.56 (1 H, dd, *J*/Hz: 2.2 and 8.2, 6-H) (Found: C, 68.45; H, 5.35; N, 12.1. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.25%).

Methyl trans-6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*carboxylate* **40**.—The bicyclo compound **37** (492 mg, 2.16 mmol) was added to a solution of sodium (298 mg, 12.95 mmol) in methanol (5 ml) and the mixture was stirred at ambient temperature for 40 h. After neutralisation, the solution was concentrated and partitioned between water and dichloromethane. The organic phase was separated, dried and evaporated to yield a white solid which was chromatographed [ethyl acetate–hexane (3:1)] to give methyl *trans*-4-amino-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-carboxylate **38** (176 mg, 31%), which was used without further purification, δ 1.3 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 1.57 (2 H, m, NH_2), 2.6 (1 H, d, *J*/Hz: 11, 3-H), 3.77 (3 H, s, CO_2Me), 4.2 (1 H, bd, *J*/Hz: 11, 4-H), 6.73 (1 H, d, *J*/Hz: 8.5, 8-H), 7.33 (1 H, dd, *J*/Hz: 8.5 and 2, 7-H) and 7.83 (1 H, d, *J*/Hz: 2, 5-H).

Acylation of compound **38** (66 mg, 0.254 mmol) with chlorobutyryl chloride (0.029 ml, 0.254 mmol) as described for compound **24** gave methyl *trans*-4-(4-chlorobutyrylamido)-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-carboxylate **39** (93 mg, 100%) which was cyclised as described for compound **26** to give the *title compound* **40** (86%), as a white solid, m.p. 133–134 °C; ν_{max}(KBr)/cm^{-1} 2220, 1735, 1685, 1607 and 1488; δ 1.45 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 2.08 (2 H, quin, *J*/Hz: 7.4, NCH_2CH_2), 2.52 (2 H, m, CH_2CO), 3.02 (1 H, m, HCN + 1 H, d, *J*/Hz: 12.5, 3-H), 3.31 (1 H, dd, *J*/Hz: 16.5 and 7.4, HCN), 3.76 (3 H, s, CO_2Me), 5.70 (1 H, d, *J*/Hz: 12, 4-H), 6.91 (1 H, d, *J*/Hz: 8.5, 8-H), 7.31 (1 H, d, *J*/Hz: 1.4, 5-H) and 7.46 (1 H, dd, *J*/Hz: 8.5 and 1.4, 7-H) (Found: C, 65.45; H, 6.1; N, 8.4. $C_{18}H_{20}N_2O_4$ requires C, 65.85; H, 6.15; N, 8.55%).

trans-6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*carboxylic Acid* **41**.—Lithium iodide (290 mg, 2.16 mmol) was added to a solution of compound **40** (500 mg, 1.52 mmol) in collidine (16 ml) and the mixture was heated at 120–130 °C for 30 min. The mixture was cooled, diluted with 2M HCl and extracted with dichloromethane. The product was isolated by extraction into aqueous $NaHCO_3$ and reprecipitation with 2M HCl to give the *title compound* **41** (366 mg, 77%), m.p. 240–241 °C; ν_{max}(KBr)/cm^{-1} 3700–2300, 2225, 1730, 1690, 1670, 1650 and 1575; δ 1.47 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 2.1 (2 H, m, $CH_2CH_2CH_2$), 2.65 (2 H, m, CH_2CO), 2.97 (1 H, d, *J*/Hz: 12.1, 3-H), 3.0 (1 H, m, CHN), 3.40 (1 H, q, *J*/Hz: 8, CHN), 5.77 (1 H, d, *J*/Hz: 12, 4-H), 6.92 (1 H, d, *J*/Hz: 8.5 Hz, 8-H), 7.30 (1 H, d, *J*/Hz: 1.6, 5-H), 7.48 (1 H, dd, *J*/Hz: 8.5 and 1.9, 7-H) and 8.3 (1 H, br, CO_2H) (Found: C, 64.7; H, 5.95; N, 8.65. $C_{17}H_{18}N_2O_4$ requires C, 64.95; H, 5.75; N, 8.9%).

trans-6-*Cyano*-3,4-*dihydro*-3-*hydroxymethyl*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **42**.—A mixture of lithium borohydride (50.7 mg, 2.36 mmol), compound **40** (500 mg, 1.52 mmol) and methanol (75.6μl, 2.36 mmol) in ether (80 ml) was heated under reflux for 5.5 h and then cooled. After washing with 2M HCl the ethereal phase was dried and evaporated to give a white foam which, after chromatography [cyclohexane–ethyl acetate (1:4) to ethyl acetate], gave the *title compound* **42** (190 mg, 46%), m.p. 198–199 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 3600–3300, 2240, 1670, 1610 and 1580; δ 1.39 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 1.84 (1 H, dd, *J*/Hz: 12 and 2, 3-H), 2.12 (2 H, quin, *J*/Hz: 7, $CH_2CH_2CH_2$), 2.61 (2 H, m, CH_2CO), 3.07 (2 H, t, *J*/Hz: 7, CH_2N), 3.35 (1 H, m, OH). 3.54 (1 H, dd, *J*/Hz: 11.2 and 3.5, CHOH), 3.80 (1 H,d, *J*/Hz: 13, CHOH), 5.50 (1 H, d, *J*/Hz: 12.1, 4-H), 6.90 (1 H, d, *J*/Hz: 8.5, 8-H), 7.34 (1 H, br s, 5-H) and 7.46 (1 H, dd, *J*/Hz: 8.5 and 1.5, 7-H) (Found: M$^+$, 300.1474. $C_{17}H_{20}N_2O_3$ requires M, 300.1474).

trans-6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran*-3-*carbaldehyde* **43**.—Benzeneselenenic anhydride (54 mg, 0.15 mmol) and compound **42** (45 mg, 0.15 mmol) in dry THF (5 ml) were heated under reflux for 4 h and then cooled. Removal of the solvent and chromatography (ethyl acetate) gave the *title compound* **43** (36 mg, 83%), m.p. 180–181 °C; ν_{max}(KBr)/cm^{-1} 2225, 1723, 1684, 1611 and 1577; δ 1.5 (3 H, s, CH_3), 1.6 (3 H, s, CH_3), 2.1 (2 H, m, $CH_2CH_2CH_2$), 2.5 (2 H, m, CH_2CO), 2.9 (1 H, dd, *J*/Hz: 12 and 4, 3-H), 3.1 (2 H, m, CH_2N), 5.9 (1 H, d, *J*/Hz: 12, 4-H), 6.96 (1 H, d, *J*/Hz: 9, 8-H), 7.4 (1 H, d, *J*/Hz: 2, 5-H), 7.55 (1 H, dd, *J*/Hz: 9 and 2, 7-H), 9.75 (1 H, d, *J*/Hz: 4, CHO) (Found: M$^+$, 298.1331; C, 68.4; H, 6.25; N. 9.1. $C_{17}H_{18}N_2O_3$ requires M, 298.1317; C, 68.45; H, 6.1; N, 9.4%).

trans-6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-3-*methoxymethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **44**.—Iodomethane (0.022 ml, 0.350 mmol) was added to a mixture of compound **42** (70 mg, 0.233 mmol) and NaH (80% dispersion in mineral oil; 7.7 mg, 0.256 mmol) in dry THF (5 ml) and the mixture heated under reflux for 1.5 h. Additional iodomethane (0.088 ml, 1.4 mmol) and NaH (15.4 mg, 0.512 mmol) were added and heating maintained for a further 1.5 h. The mixture was cooled and evaporated and the residue chromatographed (ethyl acetate) to give the *title compound* **44** (63 mg, 86%), m.p. 92 °C; ν_{max}(KBr)/cm^{-1} 2225, 1690–1680, 1610 and 1575; δ 1.26 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 1.85–2.3 (3 H, m, $CH_2CH_2CH_2$ + 3-H), 2.4–2.65 (2 H, m, CH_2CO), 2.8–3.2 (2 H, m, CH_2N), 3.33 (3 H, s, OCH_3), 3.4 (2 H, d, *J*/Hz: 5, CH_2O), 5.37 (1 H, d, *J*/Hz: 8, 4-H), 6.9 (1 H, d, *J*/Hz: 8, 8-H), 7.34 (1 H, d, *J*/Hz: 2, 5-H) and 7.5 (1 H, dd, *J*/Hz: 8 and 2, 7-H) (Found: M$^+$, 314.1640; C, 68.75; H, 7.15; N, 8.85. $C_{18}H_{22}N_2O_3$ requires M, 314.1630; C, 68.75; H, 7.05; N, 8.9%).

trans-6-*Cyano*-3-*fluoromethyl*-3,4-*dihydro*-2,2-*dimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **45**.—To a stirred solution of compound **42** (95 mg, 0.317 mmol) in dichloromethane (2.5 ml) was added DAST (39.6 mg, 0.317 mmol) in dichloromethane (1 ml) dropwise at −70 °C. The mixture was allowed to reach room temperature and stirring continued for 18 h before evaporation of the solvent. Chromatography (ethyl acetate) gave the *title compound* **45** (25 mg, 30%), m.p. 159–160 °C; ν_{max}(KBr)/cm^{-1} 2235, 1680, 1610 and 1580; δ 1.3 (3 H, s, CH_3), 1.6 (3 H, s, CH_3), 2.1 (3 H, m, 3-H + $CH_2CH_2CH_2$), 2.55 (2 H, m, CH_2CO), 2.85–3.35 (2 H, m, CH_2N), 4.40 (2 H, dd, *J*/Hz: 48 and 5, CH_2F), 5.32 (1 H, d, *J*/Hz: 12, 4-H), 6.9 (1 H, d, *J*/Hz: 9, 8-H), 7.3 (1 H, d, *J*/Hz: 2, 5-H) and 7.5 (1 H, dd, *J*/Hz: 9 and 2, 7-H) (Found: M$^+$, 302.1426. $C_{17}H_{19}FN_2O_2$ requires M, 302.1431).

trans-6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-3,4-*bis*-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzopyran* **46**.—

(*a*) *From compound* **1**. Powdered cromakalim **1** (572 mg, 2 mmol) was added to a solution of potassium t-butoxide (440

mg, 4 mmol) in pyrrolidinone (10 ml) and the mixture was stirred at 100 °C for 5 h. The mixture was cooled, poured into water and the product was extracted into chloroform. Evaporation of the dried extract gave the *title compound* **46** (405 mg, 57%), m.p. 256–258 °C (ethyl acetate); ν_{max}(Nujol)/cm^{-1} 2235, 1690, 1680, and 1120; δ 1.30 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 2.07 (4 H, m, 2 × $CH_2CH_2CH_2$), 2.30 (4 H, m, 2 × CH_2CO), 2.93 (1 H, m, CH_2N), 3.33 (2 H, m, CH_2N), 3.67 (1 H, m, CH_2N), 4.70 (1 H, d, *J*/Hz: 12, 4-H), 5.67 (1 H, d, *J*/Hz: 12, 3-H), 6.95 (1 H, d, *J*/Hz: 9, 8-H), 7.30 (1 H, br s, 5-H) and 7.53 (1 H, dd, *J*/Hz: 9 and 3, 7-H) (Found: C, 67.65; H, 6.7; N, 11.9. $C_{20}H_{23}N_3O_3$ requires C, 67.95; H, 6.55; N, 11.9%).

(*b*) *From compound* **7**. A similar reaction of benzopyran **7** with pyrrolidinone anion at 100 °C for 1 h gave a 71% yield of the bis(oxopyrrolidinyl) compound **46**, identical with that obtained above. In this instance, 6% of 6-*cyano*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran*-4-*one* **48**, m.p. 122–124 °C, ν_{max}(Nujol)/cm^{-1} 2220, 1690 and 1665; δ 1.49 (6 H, s, 2 × CH_3), 2.78 (2 H, s, CH_2), 7.30 (1 H, d, *J*/Hz: 8.9, 8-H), 7.68 (1 H, dd *J*/Hz: 1.8 and 8.8, 7-H) and 8.18 (1 H, d, *J*/Hz: 1.8, 5-H) (Found: C, 71.8; H, 5.5; N, 6.95. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 6.95%) and 6% of unchanged benzopyran **7** were also recovered.

6-*Cyano*-2,2-*dimethyl*-3-*nitro*-2H-1-*benzopyran*-4-*one* **47**.—Fuming nitric acid (193.8 μl, 4.4 mmol) was added to a soluiton of the benzopyran **7** (268 mg, 1 mmol) in acetonitrile (10 ml) at −30 °C. The reaction mixture was stirred at −20 °C for 65 h, quenched with aqueous sodium hydrogen carbonate and extracted into ethyl acetate. The combined organic layers were washed with aqueous sodium hydrogen carbonate, dried and evaporated. The residue was chromatographed [ethyl acetate–hexane (4:1)] to give the ketone **48** (6 mg, 3%) followed by the *title compound* **47** (80 mg, 33%), ν_{max}(CH_2Cl_2)/cm^{-1} 2230, 1720, 1612, 1560, 1482, 1420 and 1300–1250; δ 1.6 (3 H, s, CH_3), 1.7 (3 H, s, CH_3), 5.28 (1 H, s, 3-H), 7.22 (1 H, d, *J*/Hz: 9, 8-H), 7.94 (1 H, dd, *J*/Hz: 9 and 2, 7-H) and 8.37 (1 H, d, *J*/Hz: 2, 5-H).

Further elution afforded starting benzopyran **7**, (101 mg, 38%).

6-*Cyano*-3,4-*dihydro*-2,2-*dimethyl*-3,3-*dinitro*-2H-1-*benzopyran*-4-*ol* **49**.—Iodine (1.14 g, 4.5 mmol) was added to a solution of compound **36** (555 mg, 3 mmol), $NaNO_2$ (0.827 g, 12 mmol) and ethylene glycol (0.558 g, 9 mmol) in water (1.25 ml) and ethyl acetate (9.4 ml) at 0 °C. The mixture was stirred at ambient temperature for 5 d and extracted with ethyl acetate. The extracts were washed with aqueous sodium thiosulphate, dried, and evaporated and the residue chromatographed (dichloromethane to ethyl acetate) to give starting material **36** (400 mg) followed by the *title compound* **49** (220 mg, 25%) as an oil, ν_{max}(CH_2Cl_2)/cm^{-1} 3525, 3300, 2225, 1630, 1605, 1480 and 1280; δ 1.36 (3 H, s, CH_3), 1.62 (3 H, s, CH_3), 5.95 (1 H, s, 4-H), 7.05 (1 H, d, *J*/Hz: 8.5, 8-H), 7.61 (1 H, dd, *J*/Hz: 8.5 and 2, 7-H), 8.3 (1 H, d, *J*/Hz: 2, C 5-H) and 9.8 (1 H, s, OH).

Cis- *and* trans-4-*Acetamido*-6-*cyano*-3,4-*dihydro*-2,2-*dimethyl*-3-*nitro*-2H-1-*benzopyran* **52** *and* **53**.—Nitronium tetrafluoroborate (399 mg, 3 mmol) was added to a solution of the benzopyran **37** (555 mg, 3 mmol) in acetonitrile (10 ml) at 0 °C and the reaction mixture was stirred for 24 h at ambient temperature. It was then diluted with water and extracted with ethyl acetate. The dried organic phase was evaporated and the residue chromatographed [dichloromethane to dichloromethane–ethyl acetate (1:1)] to give the starting benzopyran **37** (61 mg, 11%) followed by a mixture of the *cis–trans* isomers **52** and **53** (1:1, 408 mg, 47%). Further chromatography [hexane to hexane–ethyl acetate (1:1)] gave the cis-*isomer* **52** (120 mg, 14%), m.p. 200–201 °C; ν_{max}(KBr)/cm^{-1} 2230, 1670, 1610, 1580, 1568, 1555, 1535, 1493 and 1380; δ ([$^2H_6$]DMSO) 1.41 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 1.96 (3 H, s, $COCH_3$), 5.44 (1 H, d, *J*/Hz: 5.8, 3-H), 5.55 (1 H, dd, *J*/Hz: 6.6 and 7.1, 4-H), 7.03 (1 H, dd, *J*/Hz: 6.6 and 2.2, 7-H), 7.71 (1 H, d, *J*/Hz: 6.9, 8-H), 7.72 (1 H, d, *J*/Hz: 2.2, 5-H), 8.53 (1 H, d, *J*/Hz: 7.1, NH) (Found: C, 58.05; H, 5.15; N, 14.4. $C_{14}H_{15}N_3O_4$ requires C, 58.15; H, 5.25; N, 14.5%)

This was followed by the trans-*isomer* **53** (120 mg, 14%), m.p. 229–231 °C; ν_{max}(KBr)/cm^{-1} 3365, 2233, 1663 and 1554; δ ([$^2H_6$]DMSO) 1.38 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 1.93 (3 H, s, CH_3CO), 5.14 (1 H, d, *J*/Hz: 7.7, 3-H), 5.51 (1 H, dd, *J*/Hz: 7.7 and 8, 4-H), 7.06 (1 H, d, *J*/Hz: 9.4, 7-H), 7.7 (2 H, m, 5-H, 8-H), 8.65 (1 H, d, *J*/Hz: 7.7, NH) (Found: C, 58.1; H, 5.4; N, 14.3. $C_{14}H_{15}N_3O_4$ requires C, 58.15; H, 5.25; N, 14.5%).

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