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SYNTHESIS OF HOMOCHIRAL POTASSIUM CHANNEL OPENERS: ROLE OF THE BENZOPYRANYL 3-HYDROXYL GROUP IN CROMAKALIM AND PYRIDINE N-OXIDES IN DETERMINING THE BIOLOGICAL ACTIVITIES OF ENANTIOMERS

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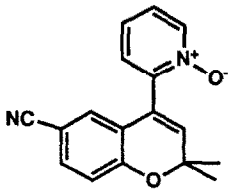
Abstract: The preparation of several homochiral benzopyranyl potassium channel openers is described. A subtle stereochemical effect of the 3-hydroxyl group on the biological activities of the enantiomers was observed .

Potassium channel openers such as cromakalim and pinacidil represent a novel class of smooth muscle relaxants which show promise in a variety of cardiovascular and bronchopulmonary diseases.[1] We have recently reported on the design[2] and synthesis[3] of the potassium channel activator Ro 31-6930 (**1**), which we believe binds to the same receptor as cromakalim.



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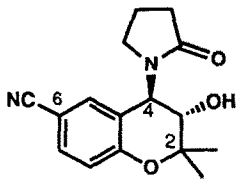

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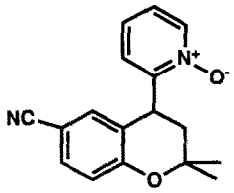
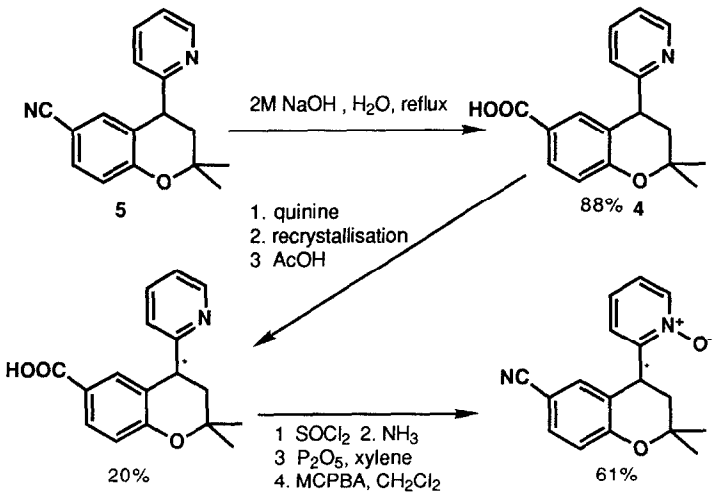


3

This compound lacks a chiral centre, unlike cromakalim (rac-**2**),[4] so obviously the issue of differential activities of enantiomers does not arise. We were also interested in the dihydrobenzopyran derivative **3** which possesses a single chiral centre. The potent activity of racemic **3** encouraged us to obtain the separate enantiomers. We report here the preparation of the enantiomers of **3** and a general method for generating systems of this type in homochiral form of known absolute configuration. An explanation of a subtle stereochemical effect in this series of potassium channel activators is provided. The results are correlated with the absolute configurations of the enantiomers of cromakalim.

We felt in this case that the most expedient way of obtaining large quantities of single enantiomers would be by resolution. For **3** this was achieved by resolution of the carboxylic acids **4** as shown in scheme 1. The nitriles **5** were hydrolysed to the carboxylic acids **4**. Diastereomeric salts were formed with quinine. One preferentially crystallised from ethyl acetate. The crystals were converted back to one homochiral free acid by treatment with acetic acid. The other enantiomerically enriched acid was liberated from the mother liquors with acetic acid and then the free acid treated with (S)-1-(1-naphthyl)ethylamine. One of the diastereomeric salts crystallised from acetone. Liberation of the free acid now furnished the other enantiomer (not shown). The two acids were separately converted through to the homochiral nitriles and oxidation gave the required N-oxides.[5]



SCHEME 1

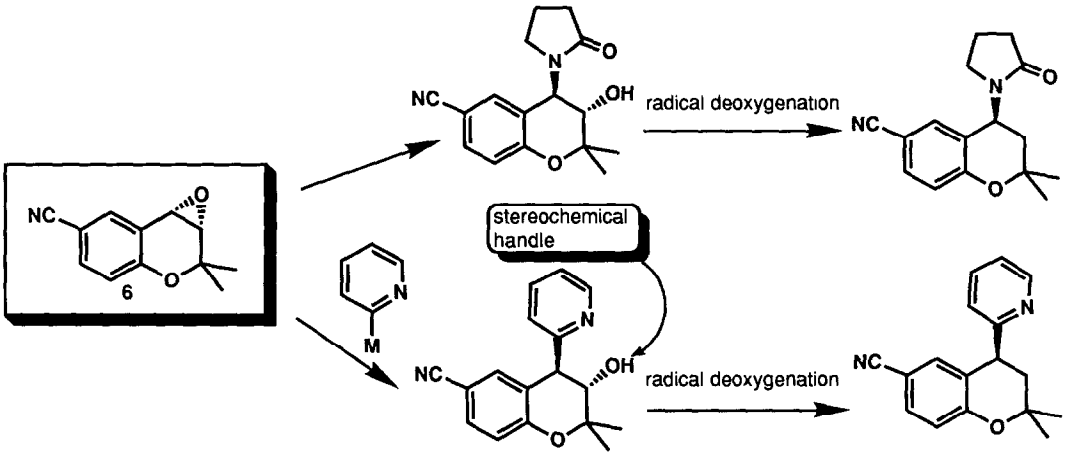
The potassium channel opening activities are presented in Table 1.[6] In contrast to the 100 fold difference in activity between the enantiomers of cromakalim (entry 4A vs. 4B), in the N-oxide case only a 3 fold separation was observed (entry 1A vs 1B) representing a contravention of Pfeiffer's rule [7] This created two problems:

1 A close correlation in activities had previously been observed between the N-oxides and the lactams which had been interpreted as an indication of binding to the same receptor[2] - this was now in doubt.

2 We had assumed that the distomers of the racemates studied were virtually inactive and that the eutomers had the same absolute configuration. With such similar activities for the enantiomeric N-oxides this could no longer be assumed.

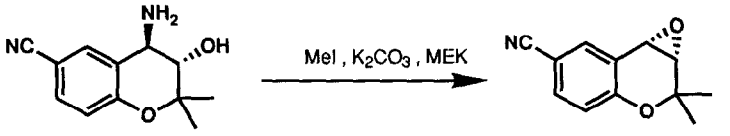
Consideration of the chemical structures studied led us to the conclusion that perhaps the 3-hydroxyl, absent in **3** but present in **2**, was responsible for the difference. We therefore set ourselves the target of preparing the deoxy derivatives of cromakalim and the *trans* 3-hydroxy derivatives of **3** in their homochiral forms and in such a way that their absolute configurations could be compared.

As cromakalim had been obtained from the racemate of the epoxide **6**[8] it seemed reasonable that reaction of this epoxide with a suitable pyridyl organometallic reagent might generate the required hydroxy compounds (scheme 2). Further, if the enantiomers of the epoxide were used then a correlation between the absolute stereochemistry of the lactams and the corresponding N-oxides would be available Radical deoxygenation[9] of the 3-hydroxy groups as shown in scheme 2 would generate the required deoxy derivatives in their homochiral forms The homochiral epoxides also have the advantage that the hydroxyl in the product from nucleophilic attack would provide a "stereochemical handle" to follow the course of the benzopyran-pyridine/lactam bond forming reaction. We felt that this was essential to enable us to observe any retention of configuration at the benzylic centre leading to mixtures of epimers.



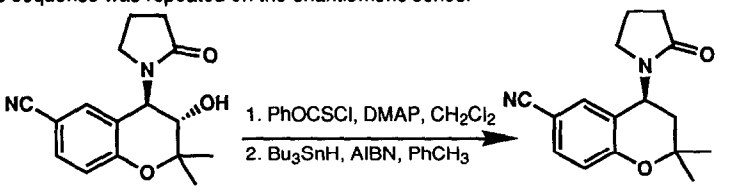
SCHEME 2

The epoxides were prepared easily and in large quantities, as shown in scheme 3, from the resolved amino alcohols,[10] the absolute configurations of which had been established by conversion through to lactams of known absolute configuration.[11]



SCHEME 3

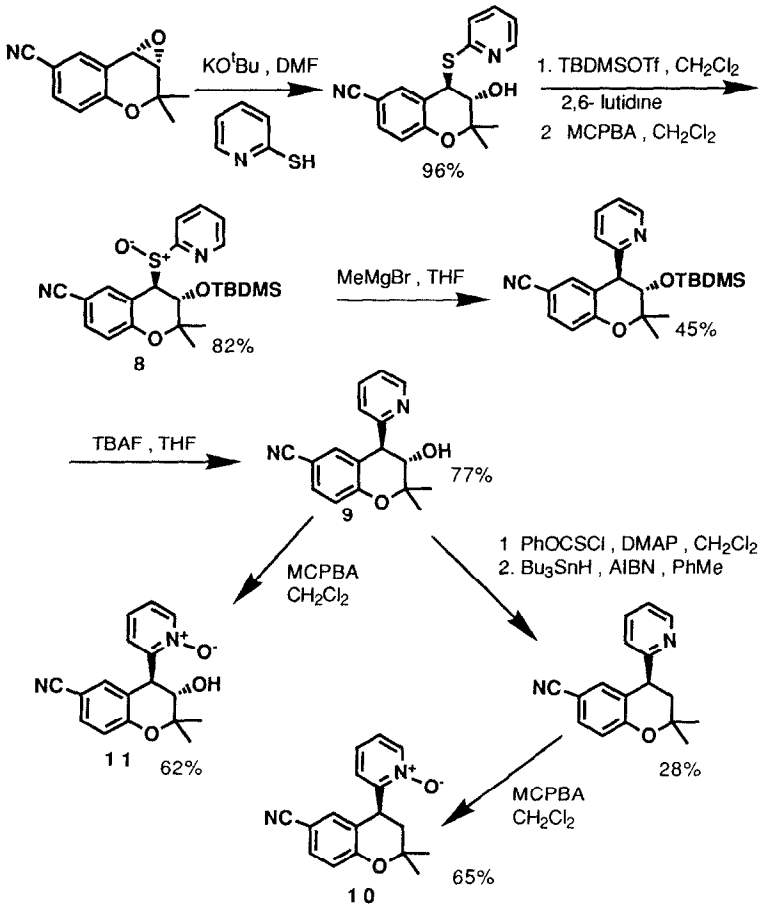
Homochiral amino-alcohol was converted through to homochiral lactam using the procedure developed by the Beecham group for the racemate.[12] As predicted radical deoxygenation afforded the homochiral deoxy lactam (see scheme 4). This sequence was repeated on the enantiomeric series.[5]



SCHEME 4

To prepare the homochiral N-oxides the initial intention had been to open the epoxide with a pyridyl organometallic reagent, but although a variety of conditions and metals were used none of the required product was obtained. It had been reported that pyridyl benzyl sulphoxides on treatment with Grignard reagents undergo a sulphoxide extrusion reaction to give benzyl pyridines with retention of configuration.[13] Accordingly, on treatment of the epoxide **6** with pyridine-2-thiol, nucleophilic attack occurred smoothly to give only the *trans* product. This was converted through to a mixture of sulphoxides **8** diastereomeric at the sulphur centre. We were pleased to find the latter underwent the

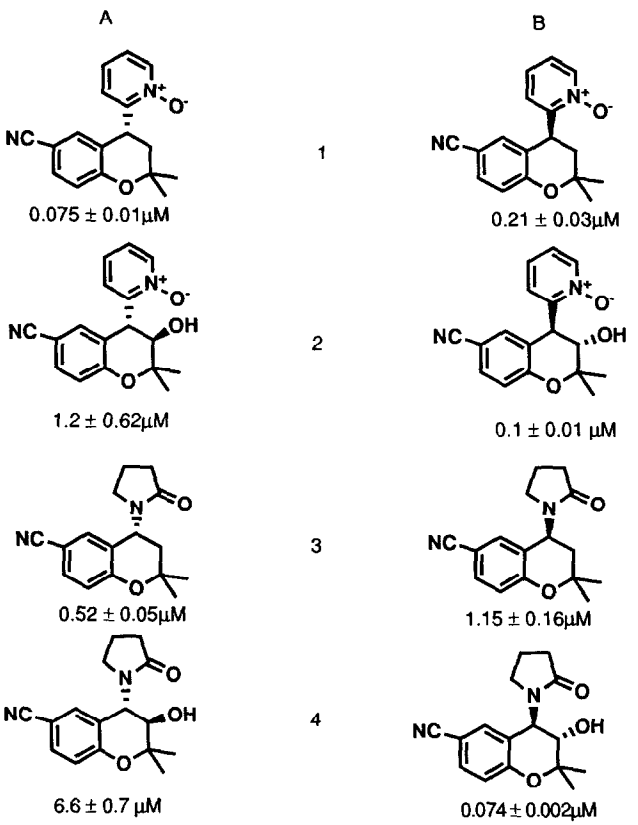
extrusion reaction with retention of configuration to give, after deprotection, the alcohol **9** (scheme 5) Alcohol **9** was then converted through to the required products **1 0** and **11** The sequence was repeated on the enantiomeric series.[5] Thus all the required compounds had been prepared to enable analysis of the effects of absolute configuration on biological activity. For the N-oxides, in contrast to the material obtained by resolution (scheme 1), the absolute configurations were now known.



SCHEME 5

The potassium channel opening activities of the eight compounds thus prepared are described in the Table 1.[6] The first point to note is that the eutomers of the two lead compounds **2** and **3** have *opposite* absolute configurations (entry 1A vs. 4B). However the parallel of activities between the lactams and the N-oxides described previously emerges once again when all the results are compared. In the absence of the hydroxyl, both N-oxides and lactams show similarly small reductions in activity on changing absolute configurations (entry 1A vs. 1B and 3A vs 3B), that is, for the deoxy compounds the biological assay appears not to discriminate appreciably between enantiomeric forms

TABLE 1



A differential effect of the hydroxyl can be observed in each enantiomeric series. If the lactam and N-oxide are termed generically the bioisostere then for an α-configured bioisostere the introduction of a trans (β-configured) hydroxyl is detrimental to potency (~10 fold) (entry 1A vs. 2A and entry 3A vs 4A). In the β-configured bioisostere, introduction of a trans (α) hydroxyl represents a positive binding influence (entry 1B vs. 2B and 3B vs. 4B). This enhancement is much more pronounced for the lactam than the N-oxide. *It is clear from these data that the β-configured hydroxyl accounts for the chiral discrimination observed in the biological properties of the enantiomers of cromakalim.* In the absence of more structural information on the receptor it is difficult to rationalise precisely why it does not discriminate between the enantiomers when there is only one chiral centre present. The simplest explanation is that there is more than one binding site, but it is quite conceivable that both enantiomeric forms can satisfy the requirements for binding at the same site.

This example provides a warning against the use of racemates as models of activity for enantiomers. Even having established chiral discrimination in a lead compound, minor changes can lead to a breakdown in this pattern. This provides further impetus for working only with enantiomers of known configuration if one is more fully to understand drug receptor interactions. It reinforces the requirement for the development of flexible asymmetric synthetic methods so that homochiral compounds can be routinely prepared.

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biological evaluations.

References and notes:

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3. Attwood, M R; Churcher, I; Dunsdon, R M; Hurst, D N and Jones, P S; *Tetrahedron Lett.*, 1991, 32, 811.

4 All diagrams represent homochiral compounds with the absolute configuration shown.

5 The optical purity of novel compounds submitted for biological testing was established by the use of chiral HPLC; stationary phase, cellulose tris-(3,5-dimethylphenylcarbamate), Chiralcel OD™, mobile phase 15% v/v 2-propanol /hexane. With the exception of **11**, which was shown to be contaminated with 2% of its enantiomer, all compounds contained less than 0.25% of their enantiomers

6. The activities reported are IC_{50} values, i.e the concentration of test substance producing half maximal reduction of the contraction evoked by 20mM KCl in rat hepatic portal veins. For full details of the biological screen see reference 2

7. It has been stated that the ratio in activity between the eutomeric and the distomeric isomers of a drug is proportional to potency (Pfeiffer's Rule). Thus with drugs which are poorly active it is not surprising if the enantiomers are approximately equipotent. However, for highly potent chemical entities which are presumably exhibiting tight binding to the receptor it would be expected that there should be substantial discrimination reflected in the activities, Pfeiffer, C C; *Science*, 1956, 124, 29.

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