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The Synthesis of RP 65479
A Novel, Potent Potassium Channel Opener.

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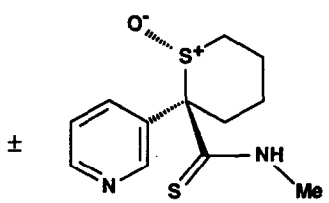
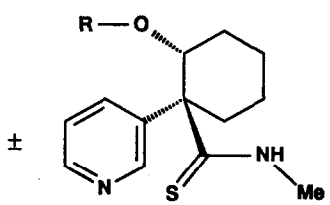
Abstract: The potent potassium channel opener, 4, RP 65479, has been synthesised from the key intermediate, 2-(3-pyridyl)cyclohexanone, 8.

Potassium channel openers have therapeutic potential in a number of disease states such as hypertension, irritable bladder syndrome and asthma.[1] We describe herein some interesting results that have been obtained as part of our synthetic chemistry programme based on 1, RP 49356, which possesses good *in vitro* inhibitory activity against K^+ induced smooth muscle cell contraction (IC_{90}= 0.8 μM).[2] Our initial objective was to investigate the change in pharmacological properties of our lead molecule by replacement of the sulphoxide group with the hydroxyl moiety, as typified by 2, and by the corresponding, more lipophilic, ether and ester derivatives, 3 and 4 respectively (Scheme 1).



RP 49356
1

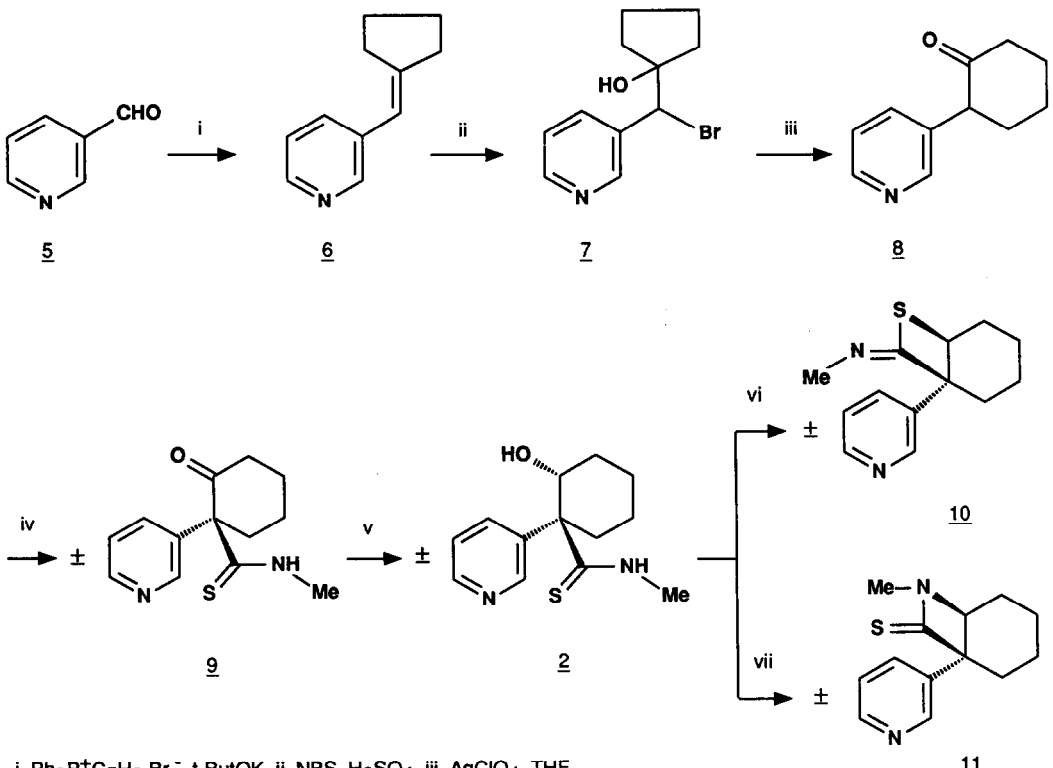


2 R= H
3 R= Me
4 R= PhCO

Scheme 1

However, the key intermediate in our strategy, 2-(3-pyridyl)cyclohexanone, 8, (Scheme 2) had not been reported in the literature, possibly because the enamine and enol ether chemistry, employed in the synthesis of the corresponding 2-pyridyl and 4-pyridyl analogues, cannot be easily extended to the 3-pyridyl series.[3] Therefore, we decided to investigate another route to 8 involving a silver cation promoted Wagner-Meerwein rearrangement[4] of the bromohydrin, 7, since we anticipated that it should be possible to generate the latter regioselectively from the olefin 6, because, in contrast to the tertiary carbon centre, the protonated pyridine ring should not stabilise, to any great extent, the developing positive charge on the adjacent cyclic bromonium ion.

Thus, commercially available pyridine-3-carboxaldehyde, 5, was converted to the olefin 6, (oil, >80%),[5] using standard Wittig chemistry. Treatment of 6 with N-bromosuccinimide in aqueous acidic medium afforded the desired bromohydrin, 7 (m.p. 91-92°C, 43% after recrystallisation). Although the yield was moderate, we were unable to detect any of the regioisomeric bromohydrin in the crude reaction mixture. The rearrangement of 7 to the novel ketone, 8 (m.p. 78-80°C, >95%) was accomplished in essentially quantitative yield using stoichiometric silver perchlorate in THF at 0°C.



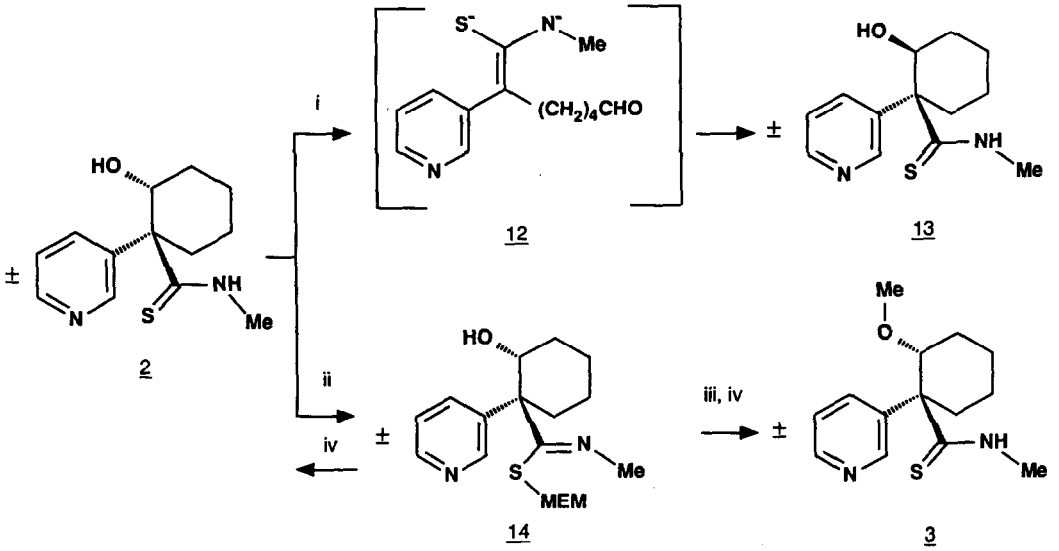
i. $Ph_3P^+C_5H_9\ Br^-$, t-ButOK. ii. NBS, H_2SO_4. iii. $AgClO_4$, THF.
iv. t-ButOK, then MeNCS. v. KBH_4, EtOH. vi. DEAD, Ph_3P, THF. vii. DEAD, Ph_3P, $HgBr_2$, THF.

Scheme 2

With this useful intermediate in hand we undertook the synthesis of 2, 3 and 4. Thus, trapping of the enolate of 8 with methyl isothiocyanate readily formed the racemic ketone thioamide, 9 (m.p. 188-190°C, >90%). Potassium borohydride reduction of 9 furnished the isomeric trans and cis alcohols, 2 (m.p. 171-3°C) and 13 (169-171°C) (Scheme 3) respectively, in a 9:1 ratio (> 90%). The initial n.m.r. assignment of the trans configuration to the alcohol 2 was reaffirmed when it was shown that, under Mitsunobu conditions,[6] only the trans isomer, 2, undergoes an intramolecular displacement reaction, forming the thioimidate, 10 (oil, 70%), or, in the presence of mercuric bromide, the thio-β-lactam, 11 (m.p. 80-82°C, 50%).

Although both the alcohols 2 and 13 were less active *in vitro* as potassium channel openers than 1, the intermediate ketone, 9, was found to be equiactive with the sulphoxide, 1, and this serendipitous discovery prompted another research programme that will be described in more detail elsewhere.

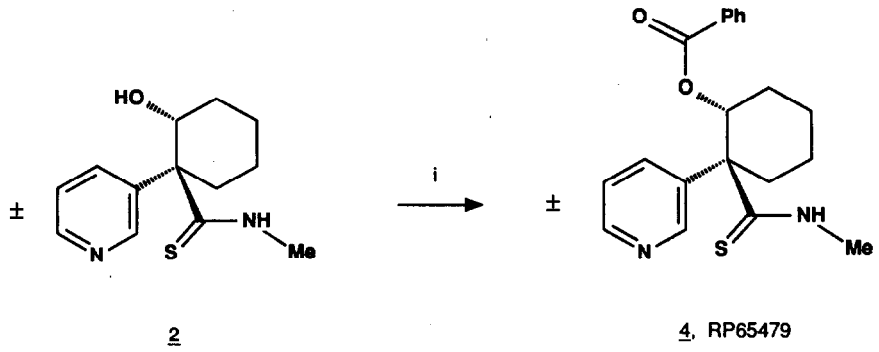
In order to prepare the ether, 3, by alkylation of the oxyanion of 2, it was necessary to protect the thioamide moiety, because this prevented not only S-alkylation, but also an isomerisation reaction from occuring. This latter, unexpected complication first arose when it was found that using two equivalents of sodium methoxide in THF at 20°C for 15 hours, both the trans alcohol, 2, and the cis alcohol, 13, could be slowly isomerised, possibly through the intermediacy of the dianion, 12, to an equilibrium mixture containing 2 and 13 in a 1:9 ratio.



i. NaOMe (2 eq.), THF. ii. NaH, THF: DMF (1:1), MEMCl. iii. NaH, MeI. iv. 0.1M HCl, THF

Scheme 3

Of the various protecting groups that we evaluated, the MEM group[7] proved to be the most suitable for our particular requirements. Thus, after conversion of 2 to the MEM thioimidate, 14 (> 90% yield), using standard conditions,[8] the starting material could be regenerated upon mild acid treatment (0.1M HCl in THF, >90%). Formation of the corresponding oxyanion of 14 followed by alkylation with methyl iodide and deprotection afforded the desired methyl ether, 3 (m.p. 168-170°C, 35% overall yield), which was found to be as active *in vitro* as 1. It is important to note that without prior protection of the thioamide group all our attempts to methylate 2 selectively at the hydroxyl function resulted in failure.



2 4, RP65479

i. PhCOOH, DCCI, DMAP, CH_2Cl_2: Pyridine (3:1)

Scheme 4.

Finally, the esterification of the trans alcohol, **2**, using benzoic acid in the presence of 1,3-dicyclohexylcarbodiimide, afforded in reasonable yield, without the need for prior protection of the thioamide function, the desired benzoate ester, **4**, RP 65479, (m.p. 211-213°C, 55% yield) (Scheme 4), which was found to be an extremely potent potassium channel opener with subnanomolar *in vitro* activity.

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3. a) Akiba K., Nishihara Y. and Wada M., *Tetrahedron Letters*, 1983, **24**, 5269-72 and refs. therein.
   b) Hamana M. and Noda H. , *Chem. Pharm. Bull. (Tokyo)*, 1967, **15**, 474-80
4. For a related Wagner-Meerwein rearrangement see Sisti A.J., *J. Org. Chem.*, 1968, **33**, 453-4.
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   b) Takahata H., Ohkura E., Ikuro K. and Yamazaki T., *Synthetic Commun.*, 1990, **20**, 285-292.
7. MEM is the acronym for the methoxyethoxymethyl group.
8. Corey E.J., Gras J.-L. and Ulrich P., *Tetrahedron Letters*, 1976, **11**, 809-12.

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