Tetrahedron Letters, Vol.31, No.17, pp 2445-2448, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF INDOLE OXAZOLINES, POTENT 5-HT_3 ANTAGONISTS

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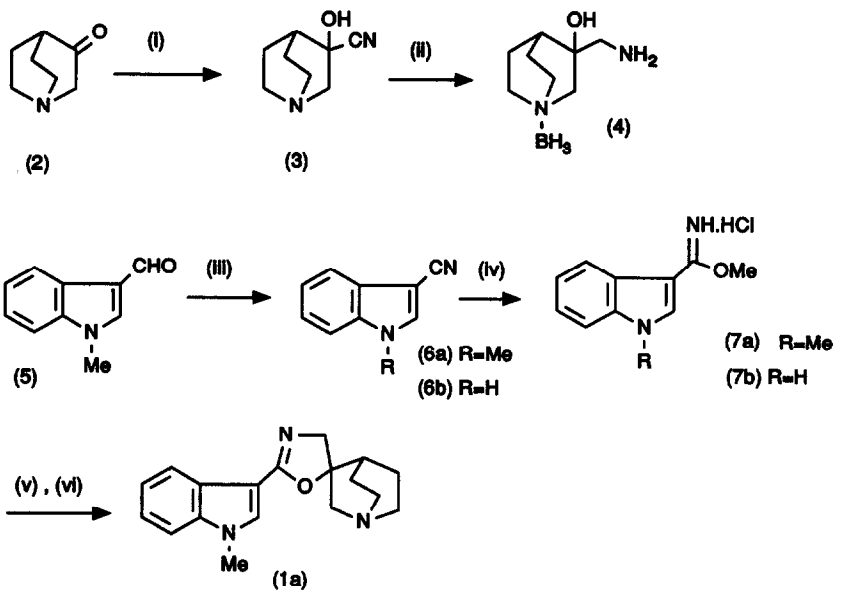
Summary The synthesis of a series of indole oxazolines is reported, proceding via addition of an azabicyclic amino alcohol, in which the azacyclic nitrogen is borane protected, to an indole imidate. Selective alkylation of the indole nitrogen is facilitated by the borane protection of the highly nucleophilic azabicyclic nitrogen.

In recent years a number of potent 5-HT_3 antagonists have been reported[1] and these compounds are thought to have potentially important therapeutic roles in cisplatin induced emesis[2], migraine[3], schizophrenia[4] and anxiety[5]. In addition, the existence of receptor heterogeneity within the 5-HT_3 subtype has been postulated[1]. As part of our programme to identify novel ligands for the 5-HT_3 receptor that would critically probe for the existence of subtypes we have prepared a series of conformationally constrained indole oxazolines (1). In this communication we report the stereoselective synthesis of these compounds, which encompasses a number of significant and novel features which includes stereocontrolled cyanohydrin formation and the use of borane as a protecting group for tertiary amines allowing regioselective alkylation of the indole nitrogen.

Reduction of the cyanohydrin[6] derived from quinuclidinone (2) with lithium aluminium hydride gave only poor yields of the desired aminoalcohol, considerable amounts of quinuclidin-3-ol being formed due to reversion of the cyanohydrin to the ketone under the basic conditions. However, the desired transformation could be achieved in high yield by reduction with three equivalents of diborane in tetrahydrofuran, the product being isolated as the crystalline borane complex (4); m.p. 163°C (ethanol); Found C , 56.65; H, 11.20; N, 16.66. $C_8H_{19}N_2OB$ requires C, 56.50; H, 11.26; N, 16.54%; δ_H (360MHz, $CDCl_3$) 1.16-1.61 (3H, m, C<u>H</u>H,CH_2), 1.86 (1H, m, CH<u>H</u>), 2.05 (1H, m, CH), 2.4-2.97 (8H, m, 4 x CH_2N); m/z (C.I) 170 (M^+).

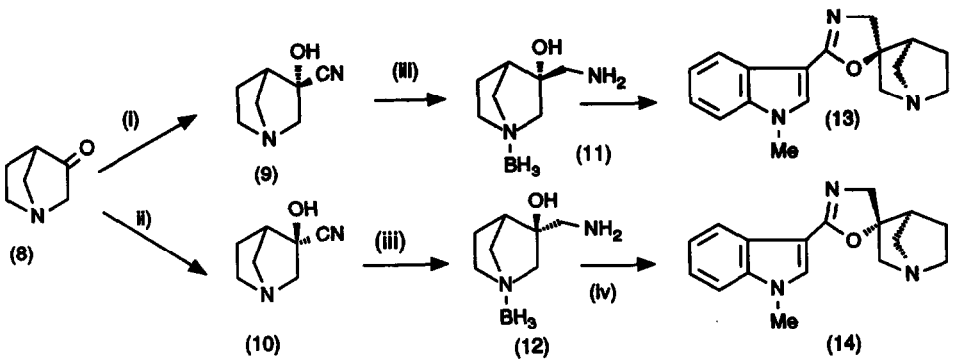
Attempts to form the desired oxazoline ring by reaction with 1-methylindol-3-carboxyl chloride failed to yield the desired product and examination of the proton nmr spectrum of the crude product suggested that under the conditions employed elimination of the tertiary alcohol had occurred to give a mixture of olefins. It was concluded that nucleophilic attack on the tertiary carbon in the cyclisation stage of the reaction was clearly disfavoured and a different strategy was investigated.



Scheme 1 : Reagents ; (i)NaCN,H_2O ; (ii) BH_3, THF ; (iii) $(H_3N)_2HPO_4$,AcOH,$PrNO_2$
(iv) MeOH , HCl ; (v) (4) , MeOH , reflux ; (vi) MeOH , HCl

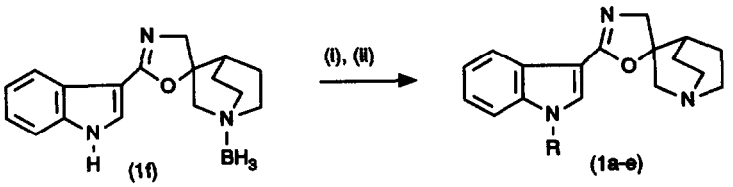
An alternative procedure was considered to be reaction of amino alcohols with imino ether hydrochlorides to form oxazolines since it is thought that the reaction proceeds via initial formation of the carbon nitrogen bond followed by cyclisation of the alcohol onto the imino ether to form the carbon oxygen bond[7]. Thus, commercially available 1-methylindole-3-carboxaldehyde (5) was first converted to the corresponding nitrile (6a), subsequent treatment with anhydrous methanolic HCl then yielded the desired methyl imidate hydrochloride (7a); m.p. 156-158°C (methanol/ether). Reaction of the imidate (7a) with the amino alcohol (4) in methanol at reflux proceeded smoothly, and in situ removal of the borane complex by treatment with methanol/HCl, gave the deprotected product (1a) as the dihydrochloride salt[8]; m.p. 261-262°C (ethanol/ether); δH (D_2O) 2.00-2.30 (3H, m, CH_2, CHH), 2.46-2.56 (1H, m, CHH), 2.70-2.74 (1H, m, CH), 3.42-3.48 (2H, m, CH_2N), 3.54-3.70 (2H, m, CH_2N), 3.84 (1H, dd, J = 15, 2.1, CHHN), 3.96 (3H, s, NMe), 4.09 (1H, d, J = 15, CHHN), 4.18 (1H, d, J = 12.3, CHHN), 4.46 (1H, d, J = 12.3, CHHN), 7.46 (1H, ddd, J = 7.5, 7.5, 1.2, H-5), 7.51 (1H, ddd, J = 7.5, 7.5, 1.0, H-6), 7.67 (1H, dd, J = 7.5, 1.2, H-7), 7.93 (1H, dd, J = 7.5, 1.0, H-4), 8.34 (1H, s, H-2); m/z 295 (M^+, freebase).

In order to probe the stereochemical requirements for binding at the 5-HT_3 antagonist binding site, an asymmetric azabicyclic system was introduced. Treatment of an aqueous solution of the hydrochloride salt of the azabicyclic ketone (8) with aqueous sodium cyanide solution whilst maintaining careful control of the temperature (< 1°C) yielded exclusively the kinetic product, the cyanohydrin (9) (Scheme 2), in which addition of the nucleophile occurred from the less hindered face of the carbonyl. In contrast, by



Scheme 2 : Reagents ; (i) NaCN, H_2O , 0 C ; (ii) NaCN , H_20 , 50 C ; (iii) BH_3 , THF ; (iv) (7a) , MeOH , reflux ; (v) MeOH , HCl.

allowing the temperature of the reaction to rise to 50°C, equilibration occurs and the epimeric thermodynamic product (10) was formed exclusively. These cyanohydrins were then converted to the corresponding oxazolines using the procedure described above to yield (13); m.p. 216-217°C and (14); m.p. 258-260°C. The stereochemistry was confirmed by 2D NOESY spectra and, in particular, a strong nOe was observed for isomer (14) between one of the methylene protons of the oxazoline ring and the methylene of the two carbon bridge of the azacycle; this was absent in isomer (13).



(15a-e) R-X = Me, Et, $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$, CH_2cPr

Scheme 3 ; Reagents ; (i) NaH, R-X, THF; (ii) MeOH/HCl

A common advanced intermediate was required for introduction of substituents into the 1- and 2-positions of the indole ring. Since direct alkylation of the indole nitrogen would be complicated by reaction with the highly nucleophilic nitrogen present in the azabicyclic system the azabicyclic nitrogen was protected by formation of the borane complex. Indole-3-carbonitrile (6b) (Scheme 1) was first converted to the imidate (7b) and reacted with the borane protected amino alcohol (4) to give the key intermediate indole oxazoline (1f); the borane protection also had the advantage of rendering the compound non-basic easing purification by chromatography on silica eluting with CH_2Cl_2/MeOH (9:1). Substitution on the indole

nitrogen was now achieved by treatment with sodium hydride in anhydrous tetrahydrofuran and the resulting anion reacted with a number of electrophiles (15a-e). The borane complex was then decomposed by exposure to methanolic/HCl to afford the substituted indole oxazolines (1a-e) as their dihydrochloride salts in overall yields ranging from 60-90%.

In summary a flexible and versatile methodology has been developed to allow access to a series of novel and potent 5-HT_3 antagonists. In addition, this work highlights the use of borane as protecting group for tertiary amines. Full biological evaluation will be reported subsequently.

References

1. B.P. Richardson, G. Engel, P. Donatsch and P.A. Stadler Nature 316, 126, (1985).

2. U. Leibundgut and I. Lancranjan, Lancet i, 1198 (1987).

3. C. Loisy, S. Beorchia, V. Centonze, J.R. Fozard, P.J. Schechter and G.P. Tell, Cephalogia 3, 71 (1985).

4. G.P. Tell *et al* Br. J. Clin. Pharmac. 18, 279P (1984).

5. B.J. Jones, B. Costall, A.M. Domeney, M. Kelly, R.P. Naylor, N.R. Oakley and M.B. Tyers, Br. J. Pharmacol., 93, 985 (1988).

6. C.A. Grob and E. Renk, Helv. Chim. Acta, 1689 (1954).

7. M.I. Butt, D.G. Neilson, K.M. Watson and Z. Ullah, J. Chem. Soc. Perkin I, (20), 2328, (1977).

8. All final products were isolated as dihydrochloride hydrates.

Acknowledgements

We gratefully acknowledge Dr. R. Herbert for the 2.D n.m.r. studies.

(Received in UK 8 March 1990)