Tetrahedron Letters,Vol.27,No.38,pp 4651-4652,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

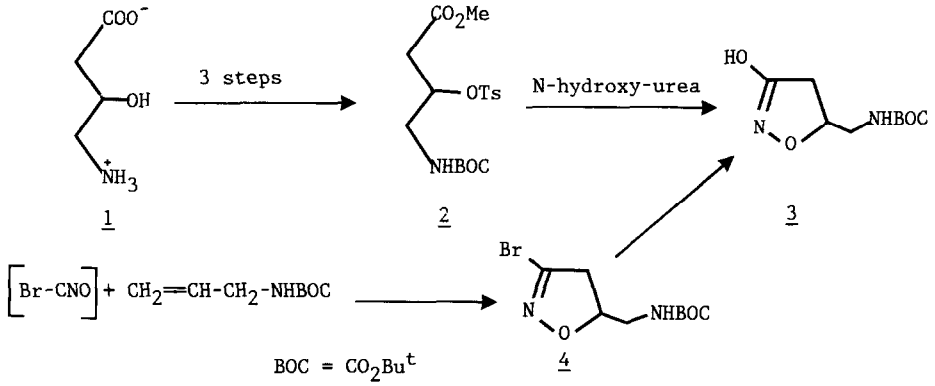
AN EASY SYNTHESIS OF DIHYDROMUSCIMOL

P.Caldirola, M.De Amici and C.De Micheli*
Istituto Chimico-Farmaceutico - Viale Abruzzi,42 -20131 Milano(Italy)

Summary: Reaction of bromonitrile oxide with N-BOC-allylamine, followed by hydrolysis with aqueous NaOH,gives isoxazolin-3-ol derivative 3, a key-intermediate in the synthesis of racemic as well as optically pure R(-)- and S(+)-dihydromuscimol.

4-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain[1]. 5-aminomethylisoxazol-3-ol(muscimol) and 5-aminomethylisoxazolin-3-ol (dihydromuscimol - DHM) are conformationally restricted analogues of GABA that have been extensively investigated[2].
They are powerful agonists at the post-synaptic GABA receptor complex but they also interact with the GABA-uptake system.
Recently[3],Krogsgaard-Larsen was able to demonstrate that the inhibitory effects on the GABA-uptake of DHM reside exclusively in the R(-)-enantiomer whereas the GABA-mimetic activity on the post-synaptic receptors is due to its S(+)-enantiomer.
The racemic form of 3, N-BOC-dihydromuscimol, was obtained in 15% yield through the reaction sequence reported in the upper part of Scheme 1[4];resolution of 3 into its enantiomers was achieved via the formation of diastereomeric salts with cinchonidine[3].

Scheme 1



1 2 3 4

In continuing our interest in the synthesis of biologically active compounds via 1,3-dipolar cycloaddition[5] , we now report an easy synthesis of 3 which allows the preparation of this key-intermediate in large quantities.
The cycloaddition of dibromoformaldoxime[6] with N-BOC-allylamine gave isoxazoline derivative 4 in 91% yield[7]; a THF solution of 4 was then reacted with a 1N NaOH solution, containing tetrabutylammonium hydrogensulfate as phase-transfer catalyst,to produce 3 in high yield[8].
The overall yield of the reaction sequence is 62%.
3 was then transformed into (R,S)-DHM according to Krogsgaard-Larsen et al.[4] by treatment with HCl.
In order to deepen the knowledge of the pharmacological profile of this interesting ligand, the preparation of its S(+)- and R(-)-enantiomers is actually underway; the results of the biological screening will be published in the next future.

Acklowdegment.Financial support from Ministero della Pubblica Istruzione (Rome) is gratefully ackowledged.

References and Notes

1. D.R.Curtis and G.A.R.Jonhston, Ergebn.Physiol., 69,97-188(1974).
2. P.Krogsgaard-Larsen,H.Hjieds, D.R.Curtis, D.Lodge and G.A.Johnston, J.Neurochem., 32,1717 (1979).
3. P.Krogsgaard-Larsen, L.Nielsen, E.Falch, D.R.Curtis, J.Med.Chem., 28, 1612 (1985).
4. P.Krogsgaard-Larsen, A.L.Nordahl-Larsen, K.Thyssen, Acta Chem.Scand.B,32,469(1978).
5. P.Caldirola, M.Ciancaglione, M.De Amici, C.De Micheli, Tetrahedron Letters, preceding paper and references cited therein.
6. D.M.Vyas, Y.Chiang and T.W.Doyle, Tetrahedron Letters, 487(1984).
7. The cycloaddition was carried out with the procedure reported in Ref.5.
8. Procedure: To a solution of 4 (600mg -2.15mmol) in THF(15ml) were added an aqueous solution of sodium hydroxide (60ml -1N) and 60mg of tetrabutylammonium hydrogensulfate. The resulting mixture was magnetically stirred and heated at 60°C until TLC disappearance of the starting material (5hr).
The reaction mixture was extracted with ether and the aqueous phase made acid with dil.HCl. After extraction (4X20ml CH_2Cl_2) and evaporation of the solvent, the residue was crystallized from n-hexane/ethyl acetate 4:1 to give 3 as colorless crystals. m.p. = 103-108°C (lit.87-92°[4] and 89-90°[9]).
Elemental analysis: required%(found%) - C 49.99(50.00) - H 7.46(7.47) - N 12.95(12.90).
The ^{1}H-NMR spectrum ($CDCl_3$) of 3 matches well with that previously reported: 8.55-8.05bs (1H-OH); 5.30-4.90bs(1H,NH); 4.90-4.45m(1H,H-5); 3.45t(2H,CH_2N); 2.85-2.50m(2H,H-4); 1.47s (9H,CMe_3).
9. L.Brehm, P.Jacobsen, J.S.Johansen and P.Krogsgaard-Larsen, J.C.S.Perkin I, 1459(1983).

(Received in UK 11 July 1986)