Total Synthesis of 3,14-Dihydroxyisomorphinans and 9α-hydroxy-3-methoxyhasubanans

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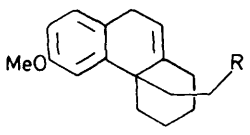
Summary Total synthesis of 3,14-dihydroxyisomorphinans and 9α-hydroxy-3-methoxyhasubanans *via* 4a-(2-aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (Ia) is described.

MUCH attention has been paid recently to the 14-hydroxy-substituted morphine derivatives[1] and their synthetic congeners[2] as potentially useful pharmacological agents. The corresponding 14-hydroxy-B/C-*trans*-fused isomers have not been reported, even though potent analgesic[3] and narcotic antagonist[4] activities have been uncovered among some of the isomorphinan structures.

We now report on the total synthesis of 3,14-dihydroxyisomorphinans and 9α-hydroxy-3-methoxyhasubanans *via* a common intermediate, the unsaturated amine (Ia), which has already been successfully employed in the synthesis of 3,14-dihydroxymorphinans.[2]

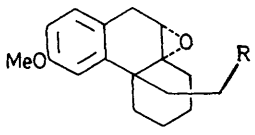
Treatment of (Ia) with ethyl chloroformate–triethylamine afforded the unsaturated urethane (Ib).† Oxidation of (Ib) with *m*-chloroperbenzoic acid afforded stereoselectively

† Satisfactory elemental analyses and n.m.r. and i.r. spectra were obtained for all new compounds.

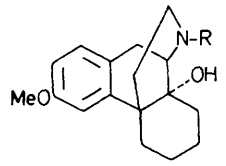


(I)

a; R = NH_2
b; R = $NHCO_2Et$
c; R = NHMe
d; R = $NMeCOCF_3$

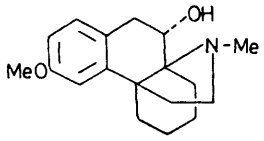


(II) R = $NHCO_2Et$
(III) R = $NMeCOCF_3$



(IV)

a; R = CO_2Et
b; R = Me
c; R = H



(V)

the α-epoxide (II). This was treated with sodium t-pentoxide in boiling benzene to effect intramolecular regioselective opening of the epoxide, and concomitant ring D formation, thus affording the 14-hydroxyisomorphinan skeleton (IVa). Reduction of (IVa) with $LiAlH_4$ afforded the *N*-methyl compound (IVb). Hydrolysis of (IVa) with KOH in boiling octan-1-ol afforded 3-methoxy-14-hydroxyisomorphinan (IVc) as an oil, HCl salt, m.p. 269—271°, which was further transformed to the various *N*-substituted 3,14-dihydroxyisomorphinans by well defined routes.[2–4] The overall yield of (IVc) from (Ia) was 55%.

Alternatively (Ib) was reduced with $LiAlH_4$ to (Ic) which was then converted into the amide (Id). Oxidation of (Id) with *m*-chloroperbenzoic acid to the α-epoxide (III), and treatment of this with K_2CO_3 in $MeOH–H_2O$ afforded a 1 : 1 mixture of (IVb) and 9α-hydroxy-3-methoxyhasubanan (V) in an overall yield of 48% from (Ia). The mixture was easily separated by column chromatography.

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