A Stereoselective Synthesis of α-Isosparteine

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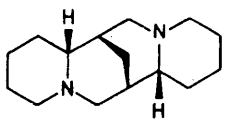
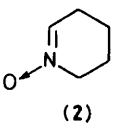
Successive cycloaddition of Δ^1-piperidiene 1-oxide to 4*H*-pyran proceeded regio- and stereo-selectively to afford a 2:1 adduct, catalytic hydrogenation of which gave α-isosparteine in high yield.

The alkaloid α-isosparteine[1] (**1**) is found in members of the *Leguminosae* family and has pharmacological activity.[2] Total syntheses of this alkaloid have been reported by several groups,[3] but all of these syntheses were nonstereoselective. In our synthetic studies on quinolizidine alkaloids,[4] we have succeeded in a stereoselective synthesis of α-isosparteine in a three-step process.

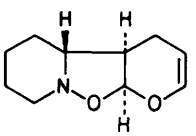
The 1,3-dipolar cycloaddition of the nitrone, Δ^1-piperidiene 1-oxide[5] (**2**), to 4*H*-pyran[6] at 140 °C gave a 1:1 adduct (**3**) with high regio- and stereo-selectivity in a 70% yield.† Further reaction of the adduct (**3**) with (**2**) at 190 °C gave a 2:1 adduct (**4**). The n.m.r. spectrum of the 2:1 adduct showed only one doublet (for an acetal proton) at δ 5.5 which was sufficiently downfield to indicate that the oxygen atoms of two molecules of the nitrone were bound to the α- and α'-positions of the 4*H*-pyran. The stereochemistry of the adduct is assumed to be *exo,trans,exo* [as in (**4**)] or *exo,cis,exo* [as in (**7**)] from the reaction mechanism. The 1,3-dipolar additions of unconjugated nitrones to enol ethers give exclusively the *exo*-addition product [*i.e.* (**4**) or (**7**)] rather than the *endo*-product [*i.e.* (**10**)] owing to steric hindrance in the transition state of the *endo* mode of addition. The *exo,cis,exo*-structure (**7**) was excluded by a control reaction. The addition of (**2**) to γ-pyrone proceeded regio- and stereo-selectively to give a single adduct [(**5**) or (**8**)] in 65% yield. Reduction of the carbonyl group with sodium borohydride proceeded stereospecifically to afford an alcohol (**6**) in quantitative yield. If the adduct had *exo,cis,exo*-stereochemistry as in (**8**), the n.m.r. signal of the carbinyl proton of (**6**) should appear as a triplet owing to coupling with the two angular protons, but instead



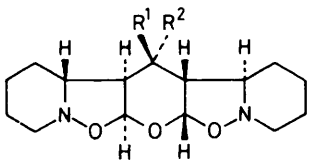
(**1**)



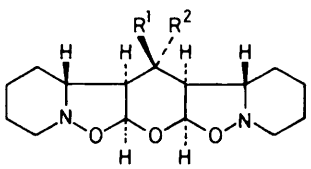
(**2**)



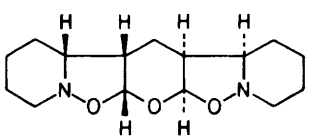
(**3**)



(**4**) $R^1 = R^2 = H$
(**5**) $R^1 = R^2 = O$
(**6**) $R^1 = OH$, $R^2 = H$



(**7**) $R^1 = R^2 = H$
(**8**) $R^1 = R^2 = O$
(**9**) $R^1 = OH$, $R^2 = H$

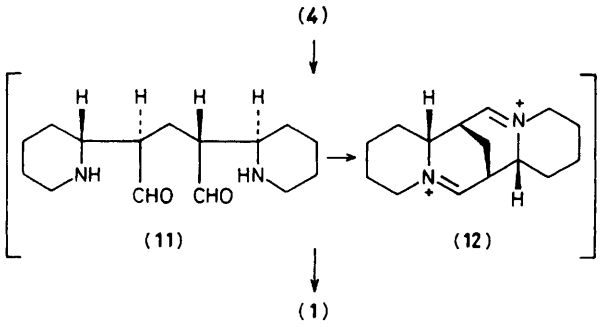


(**10**)

(**6**) showed a double doublet (*J* 5.5 and 7.5 Hz) at δ 4.10. This indicated that the adduct from γ-pyrone has the *exo,trans,exo*-stereochemistry as in (**5**), and that hydride attack on the carbonyl group of this compound from either the α- or β-side resulted in the formation of (**6**). These facts‡ suggest that the

† The yield was based on consumed 4*H*-pyran; a large amount (70%) of 4*H*-pyran was recovered. The nitrone (**2**) decomposed at the reaction temperature to δ-valerolactam and a nitrone dimer. No other cycloaddition product of 4*H*-pyran with (**2**) was detected in the reaction mixture.

‡ Attempts to convert (**5**) and (**6**) into the 4*H*-pyran adduct (**4**) were unsuccessful.



adduct from 4*H*-pyran also has *exo,trans,exo*-stereochemistry [*cf.* (**4**)].

Catalytic hydrogenation of a methanolic solution of the adduct (**4**) in the presence of palladium hydroxide gave a tetracyclic product (**1**).§ The spectral properties (i.r., mass, and ^{13}C n.m.r. spectra) agreed with those of authentic α-isosparteine.[7] Hydrogenation is considered to proceed through the intermediates (**11**) and (**12**).

§ The same reaction of the adduct (**3**) in an acidic solution afforded a mixture of α-isosparteine and sparteine.

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