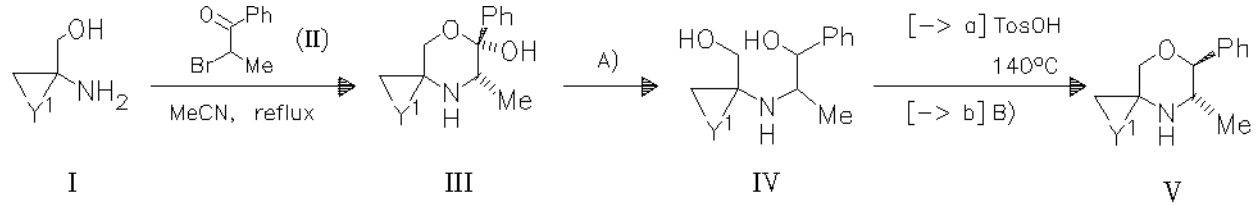
1,4-oxazine derivatives (morpholine)

R 0600

21 - 155

Synthesis, Stereochemistry and anti-Tetrabenazine Activity of Bicyclo Analogues of 2-Phenylmorpholines. — To gain further insight into the structure–activity relationship of 2-phenylmorpholines, several analogues are prepared bearing the methyl substituents encompassed into a third ring. Most of the target compounds are prepared by reaction of propiophenone (II) with the appropriate amino alcohol to give phenylmorpholinols. Alternatively, oxazines (XVII) are synthesized by alkylation of the carbinols (XIV), followed by cyclization of the resulting amino diols (XVI). Only the spiroalkanes (V) retain activity comparable to the 2-phenylmorpholines, but these compounds are 2- to 3-fold less active by the oral route of administration. — (BOSWELL, G. E.; MUSSO, D. L.; DAVIS, A. O.; KELLEY, J. L.; SOROKO, F. E.; COOPER, B. R.; J. Heterocycl. Chem. 34 (1997) 6, 1813-1820; Div. Org. Chem., Burroughs Wellcome Co., Research Triangle Park, NC 27709, USA; EN)

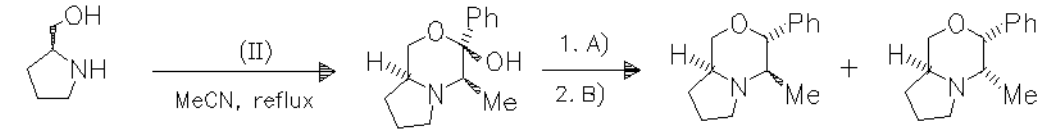


I III IV V

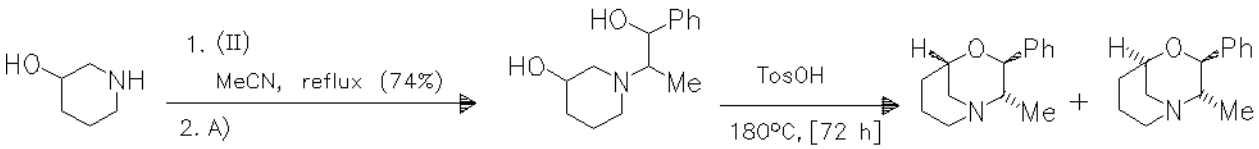
a Y^1: $-CH_2-$ –
b Y^1: $-(CH_2)_3-$ 100% (crude)

a –
b (69% from III)

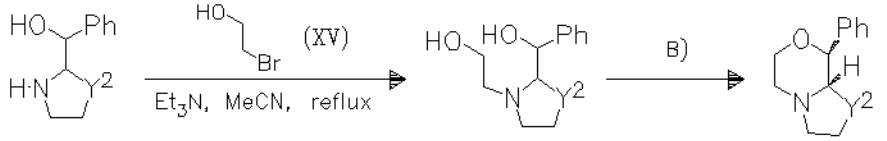
A): $NaBH_4$, EtOH, H_2O, 0 –> +25°C B): conc. H_2SO_4, CH_2Cl_2, 0 –> +25°C



(S)–(+)–VI VII* (–)–VIII* 82% (–)–IX* 10%



X XI XII 9% XIII 12%



XIV XVI XVII

a Y^2: $-CH_2-$ 58%
b Y^2: $-(CH_2)_2-$ –

a 31%
b (96% from XIVb)

A): $NaBH_4$, EtOH, H_2O, 0 –> +25°C B): conc. H_2SO_4, CH_2Cl_2, 0 –> +25°C