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THE SYNTHESIS OF THE STEREOISOMERS OF 1,X-DIMETHYL-4-OXO-1,6,7,8,9,9a-HEXAHYDRO-4H-PYRIDO[1,2-a] PYRIMIDINE-3-CARBOXAMIDES

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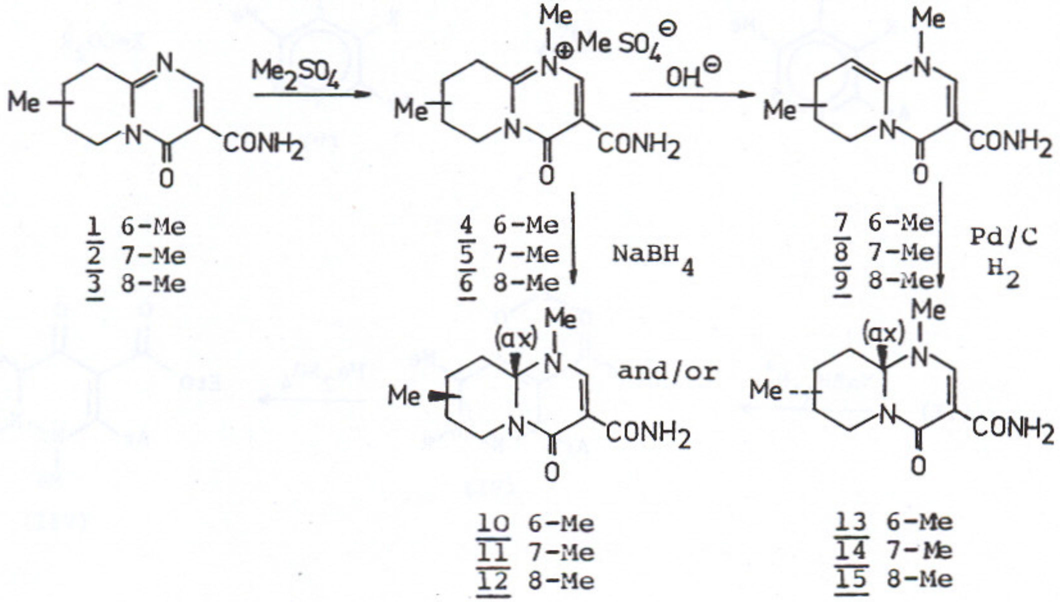
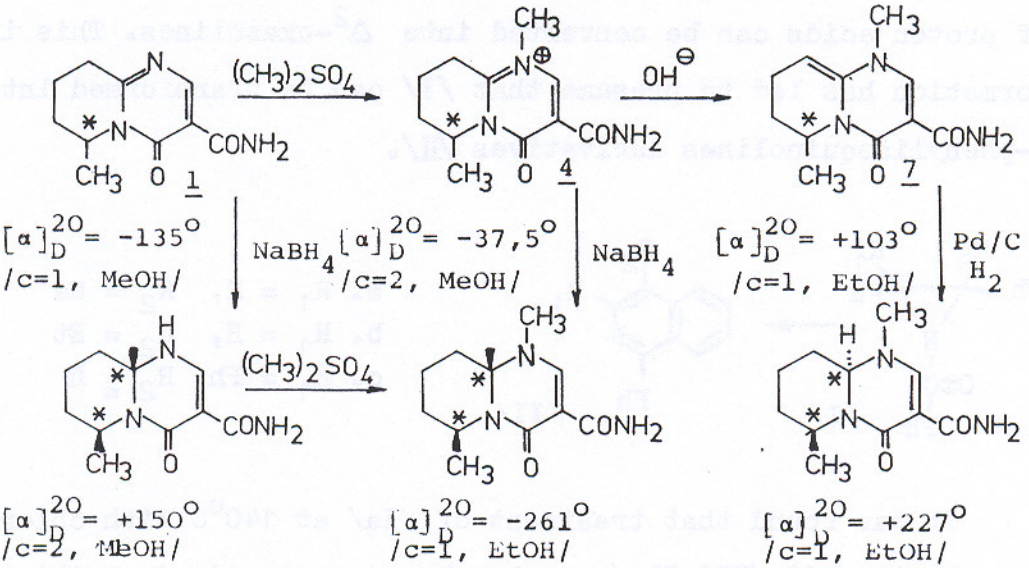
We have been studying the chemistry and pharmacology of the 4-oxo-4H-pyrido[1,2-a] pyrimidines for over ten years. The /±/1,6_{ax}-dimethyl-4-oxo-1,6,7,8,9,$9a_{ax}$-hexahydro-4H-pyrido[1,2-a] pyrimidine /10/ exhibited significant analgetic activity.

For structure—activity relationship study we aimed to synthethise 13 /the diastereomer of 10/, their optically active forms, as well as the structural isomers with the methyl-group in the 7 and 8 position. The synthetic routes are shown below.



Reduction of the quaternary salts /4,5,6/ with $NaBH_4$ /in H_2O/ resulted always in the formation of the thermodynamically more stable diastereoisomer, i.e. 10, 11 and 15 respectively, while catalytic reduction /Pd/C, MeOH/ of the enamines /7,8,9/ led to mixtures of the diastereoisomers, with ratios depending on the position of the methyl-group on the piperidine ring.

Starting from the optically active forms of the tetrahydro-derivative 1 we obtained the enantiomers of 10 and those of 13. 10 was also prepared by the alkylation of 16.



The conformation of the hexahydro-derivatives 10, 13 and 16 was investigated, by ^1H, ^{13}C NMR as well as by CD and X-ray analysis. The same pyrimidine ring conformation was found for 13 and 16, while that of 10 differed.

10 was pharmacologically more active than 13, and no difference between enantiomers was found.