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ON THE FORMATION OF THE 1-AZA-[3.1.1]-BICYCLOHEPTANE RING SYSTEM

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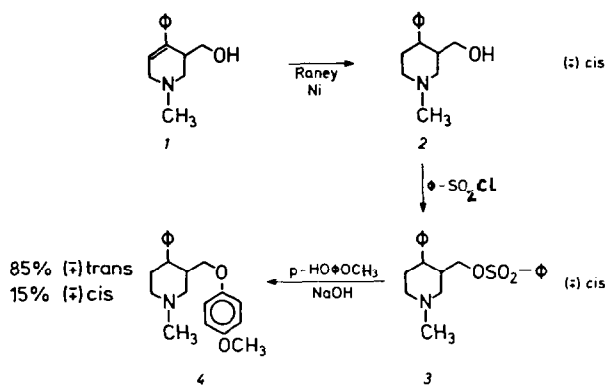
Summary: The previously unpublished bicyclic system 1-aza-[3.1.1]-bicycloheptane has been shown to exist as an unexpected intermediate in the synthesis of Femoxetine, a CNS active drug.[1]

Femoxetine (*4*) is a new potent antidepressant drug developed in our laboratory[+] during the last decade.[1] The synthesis of *4* is outlined in scheme 1.

4 exsists in four different stereoisomeric forms, where the (+)trans isomer is the active isomer. (±)trans refers to the configuration (3R*,4S*), and the term (±)cis is used to denote configuration (3R*,4R*).

In a preparation 172.4 mole (±)*1* was dissolved in 175 ℓ toluene. 1 kg Raney nickel was added and the mixture hydrogenated overnight to yield *2* as a mixture of 85% (±)cis and 15% (±)trans isomer as determined by HPLC.

The Raney nickel was removed and to the stirred solution 228.6 mole $(C_2H_5)_3N$ was added followed by 230 mole benzenesulphonyl chloride added at such a rate that the temperature was kept below 30°C. Both isomers of *2* are transformed with benzenesulphonyl chloride into the sulphoesters *3* with retained stereochemistry.



Scheme 1

The mixture was left overnight, washed with 40 ℓ of water whereafter 175 ℓ 4-methylpentanol-2, 22 ℓ NaOH 50% and 254 moles of p-methoxy-phenol were added. This mixture was refluxed for 4 hours, subsequently cooled to 25°C and treated with water (100 ℓ + 50 ℓ + 30 ℓ). The aqueous layers were discarded and the organic phase containing *4* was isolated.

Analysis of *4* by HPLC showed the composition to be 15% (±)cis and 85% (±)trans. It is therefore evident that the conversion of *3* to *4* does not proceed via the expected S_N2 mechanism.

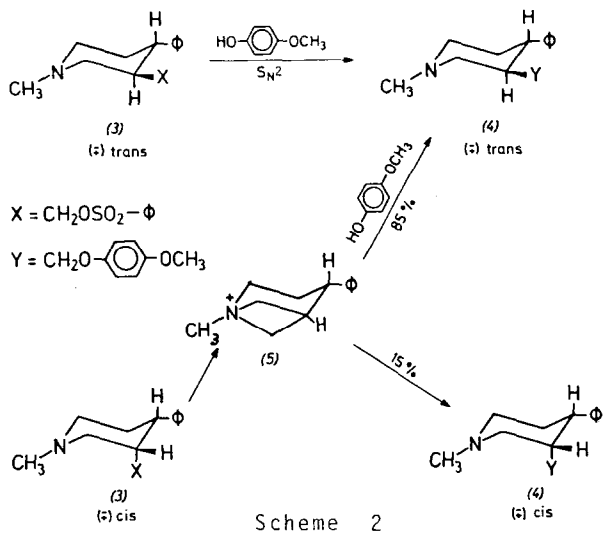
If pure (±)trans sulphoester(3) is used as the starting material in the step *3* → *4* pure (±)trans Femoxetine (*4*) is the product, indicating in this case a clean S_N2 reaction. This leads us to propose that the (±)cis isomer of *3* under the conditions described reacts via the intermediate 1-azonia-1-methyl-4-phenyl-[3.1.1]bicycloheptane cation (5) shown in scheme 2.

In order to substantiate the proposal a sample of ^{13}C labelled (±)cis sulphoester *3* was prepared[2] (scheme 3) and the step *3* → *4* was carried out as above. The enrichment in *3* was 3% determined by ^{13}C NMR in *1* and *2*.

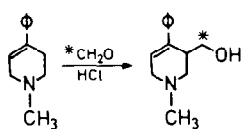
After the completion of the reaction and isolation of *4* the enrichment in *4* is found exclusively in the C(2) position of the piperidine ring. Care was taken to ensure accurate measurements of signal intensities by inserting an appropriate delay between successive accumulations.[3,4]

The cis-trans ratio observed in the reaction *3* → *4* can be envisaged as a steric effect in the bicyclic intermediate. The attack will occur from the less crowded side, opposite to the phenyl group leading to a trans configuration in *4*.

A few similar observations have been published for the azetidine structure[5,6],



Scheme 2



Scheme 3

but only for cases where the azetidinium salts have been part of larger condensed ring systems like tropane[6] and lupinine[5]. We find the observation in the present work of the highly strained bicyclic azetidine ring surprising since it is formed in presence of a strong nucleophilic agent which normally favours the S_N2 reaction pathway.

Acknowledgements

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References

1. Brit Pat. No. 1422263 21/1-1976.
2. C.A. 51, 2880f (1957).
3. ^{13}C spectra were recorded in FT Mode using Bruker 270 HX spectrometer operating with quadrature detection at 67.889 MHz. The samples were prepared as 10% w/v in $CDCl_3$ and 10 mm sample tubes were used. Spectra were accumulated with 1000 transients in 32 K data points with a spectral width of 17000 Hz with sample temperature 305 K. The antigated mode[5] was used with a pulsewidth a 7 μs (50° flip angle) and a delay between accumulations of 20 s. The (±)trans configuration of 4 gave the following data in ppm: C_2 : 59.56 (t); C_3 : 41.75 (d); C_4 : 44.18 (d); C_5 : 34.23 (t); C_6 : 56.13 (t); C_7 : 143.93; C_8,C_{12} : 127.36; C_9,C_{11} : 128.46; C_{10} : 126.37 C_{13} : 69.23 (t); C_{14} : 152.89; $C_{15}C_{19}$: 114.29; $C_{16}C_{18}$: 115.16; C_{17} : 153.46; C_{20} : 55.53 (q); C_{21} : 46.43 (q).
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