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Synthesis of Endo-2-Phenyl-7-Azabicyclo[2.2.1]heptane via High Pressure Diels-Alder Reactions of Pyrroles

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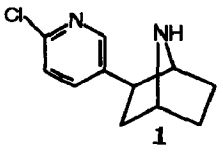
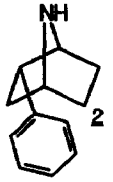
Abstract: *A straightforward route to racemic endo-2-phenyl-7-azabicyclo[2.2.1]heptane (an analogue of epibatidine) is described via the high pressure Diels-Alder reaction of 1-methoxycarbonyl-3-phenylthio-pyrrole with phenyl vinyl sulphone.*

The recent publications[1,2,3,4] of the synthesis of epibatidine (1) a novel (chloropyridyl)azabicylcoheptane with a highly potent analgesic activity[5] prompts us to disclose our results about the synthesis of the closely related endo-2-phenyl-7-azabicyclo[2.2.1]heptane (2).



1



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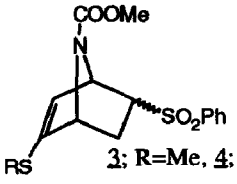


3; R=Me, 4; R=Ph

The 7-azabicycloheptane skeleton can be constructed in one step by the Diels-Alder reaction of an activated pyrrole with an electron-poor carbon carbon double-bond system. Pyrroles from which the aromaticity is reduced by an electron-withdrawing substituent on the nitrogen atom undergo Diels-Alder reactions at normal pressure with electron-poor acetylenes[6] as has been successfully applied recently in the synthesis of epibatidine[2]. Under high pressure these activated pyrroles react also with electron-poor alkenes[7,8,9] which increase the flexibility of this route to 7-azabicycloheptanes even more.

In a preceding paper we showed that 1-methoxycarbonyl-3-methylthio or -3-phenylthiopyrrole reacted easily with phenyl vinyl sulphone at 12 Kbar to 2-thiosubstituted 5-phenylsulphonyl-7-methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-enes[9] 3 and 4 in 80% yield.

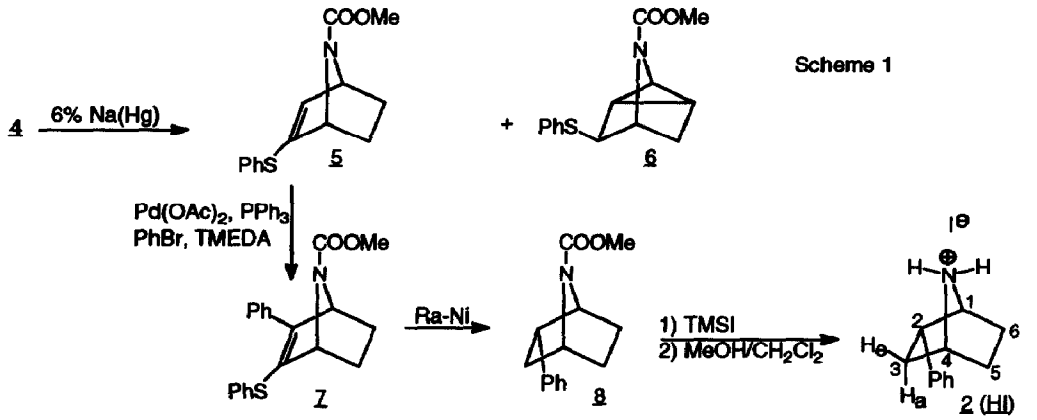
We found that compound 4 could be a useful precursor for the synthesis of 2-arylsubstituted azabicycloheptanes by the route described in scheme 1.

In the first step the phenyl sulphonyl group was removed by reduction with 6% sodium amalgam giving 5 in a moderate yield of 30%[10]. An interesting sideproduct of this reaction appeared to be the tricyclic isomer 6 which was also obtained in a yield of 25-30%.

Introduction of the phenyl group was achieved via the palladium catalyzed vinylation reaction of bromobenzene (Heck-reaction)[11] to 7 in a yield of 35-40%. Reduction of 7 with Raney Nickel gave exclusively

the endo-7-carbomethoxy-2-phenyl-7-azabicycloheptane **8** (yield 70%) as appeared from detailed analysis of the H^1-NMR spectra of **2**[12]. Removal of the carbomethoxy group with trimethylsilyl iodide led to a HI salt of **2** (containing 0.64 equivalents of HI, mp. 160-165 °C, yield 65%)[12].

Further work towards this type of biosteric analogues of epibatidine via high pressure Diels-Alder reactions of pyrroles including alternative approaches with the aryl group in the pyrrole or in the dienophile is in progress.



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H^1-NMR ($CDCl_3$): The shifts of H_1 and H_4 (3.82); H_2 (3.38) and H_{3e} (2.08) are very close to the shifts of the corresponding protons of the endo analogue[2] of epibatidine (**1**). High-resolution ms Calcd for $C_{12}H_{15}N$ (M^+): 173.12045. Found: 173.12043. HI salt of **2** (with 0.64 eq HI) mp. 160-165 °C from acetonitril. H^1-NMR ($CDCl_3$): δ(ppm)= 1.54-1.78 (m, 3H, H-5a, H-6a and H-6e), 1.74 (dd, 1H, $J_{3a,3e}$=13Hz, $J_{3a,2e}$=5.5Hz, H-3a), 1.97 (m, 1H, H-5e), 2.38 (dddd, 1H, $J_{3e,3a}$=13Hz, $J_{3e,2e}$=12.5Hz, $J_{3e,4}$=5Hz, $J_{3e,5e}$=3Hz, H-3e), 3.74 (dt, 1H, $J_{2e,3e}$=12.5Hz, $J_{2e,3a}$=5.5Hz, $J_{2e,1}$=5Hz, H-2e), 4.12 (m, 2H, H-1and H-4), 5.4 (br, NH_2^+), 7.19-7.38 (m, 5H, arom.-H).

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