THE SYNTHESIS OF 7,8-DIMETHOXY-1-(3,4-DIMETHOXYBENZYL)-2,3-DIHYDRO-1H-3-BENZAZEPINE AND RELATED COMPOUNDS

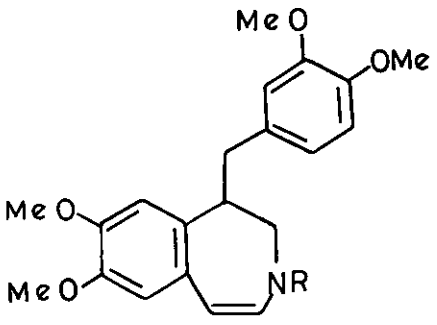
Roger F. Newton*, Malcolm Sainsbury† and Paul L.R. Stanley†

* Glaxo Group Research Limited, Ware, Hertfordshire SG12 0DJ, U.K.

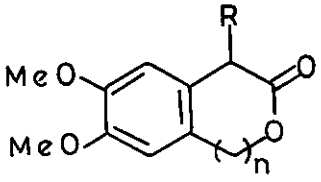
† School of Chemistry, University of Bath, Claverton Down, Bath, Avon BA2 7AY, U.K.

Abstract - The title compound has been synthesised by the acid catalysed cyclisation of 2,3-bis-(3,4-dimethoxyphenyl)propylaminoacetaldehyde diethyl-acetal. The preparation of 7,8-dimethoxy-1-(3,4-dimethoxybenzylidene)-4,5-dihydro-1H-3-benzazepine and its hydrogenation products is also described.

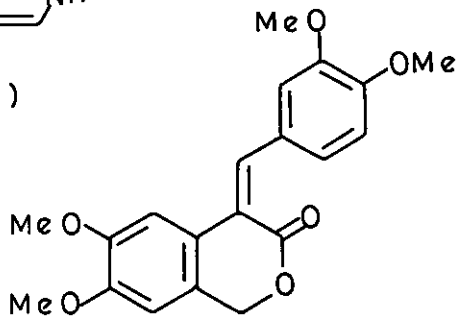
In connection with our electrochemical studies[1] we required to synthesise dihydro-1-benzyl-1H-3-benzazepines of the type (1), and, since we have previously shown that the lactone (2; R=H, n=1) can be converted into the benzyl derivative (2; R=3,4-dimethoxybenzyl, n=1) by reaction with veratraldehyde followed by hydrogenation of the product (3)[2], we considered that a similar sequence from the lactone (2; R=H, n=2) should give the homologue (2; R=3,4-dimethoxybenzyl, n=2). This compound on treatment with primary amines and reduction should give tetrahydro-1H-benzazepines which could then be selectively oxidised to the required substrates (1).



(1)

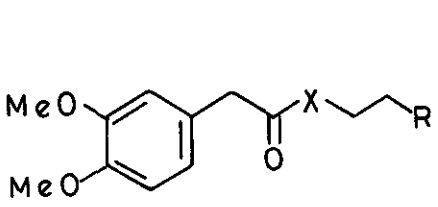


(2)



(3)

Unfortunately all attempts to cyclise the esters (4; X=O, R=OH or Br or Cl) to the lactone (2; R=H, n=2) failed as did efforts to prepare the corresponding lactam from the amide (4; X=NH, R=OH). This last compound was prepared from 2-aminoethanol and 3,4-dimethoxyphenylacetyl chloride in the presence of base (triethylamine in benzene). On one occassion when acetone was employed as solvent with potassium carbonate as the base, two products were obtained, one being the oxazolidine (5) and the other the hemiacetal (6). Since oxazolidines are readily formed from 2-aminoethanol and carbonyl compounds[3] it is likely that the first compound arises from N-acylation of preformed 2,2-dimethyloxazolidine, whereas the second product is the result of an acid catalysed reaction between the amide and acetone. The necessary acid for this process being generated in the first reaction and inadequately removed by the suspension of potassium carbonate in the dry solvent. Indeed if water is added to the reaction medium no hemiacetal is obtained.



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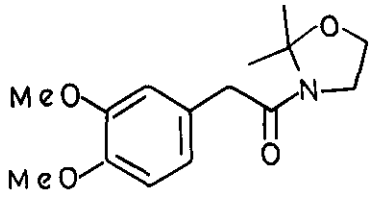

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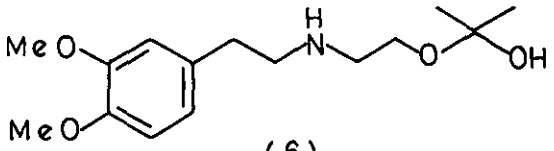
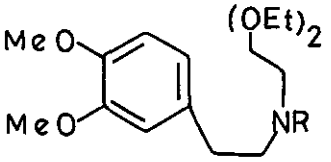


(6)

We were more successful using a modified Bobbitt[4] procedure, thus the acetal (7; R=H) and veratraldehyde when treated with 6M hydrochloric acid gave the salt (8) in 90% yield. With dilute sodium hydroxide this product afforded the corresponding free base as an unstable oil, but unlike its lower homologue in the isoquinoline series[5] the exocyclic double bond in this compound shows no tendency to migrate into the ring. Catalytic reduction of this compound over Adams' catalyst occurs in two stages, first to give the stilbene (9) and then the fully reduced azepine (10; R=H). It has not been possible to selectively oxidise the last mentioned product nor its N-methyl derivative (10; R=Me), both of which are unstable and sensitive to air and light.



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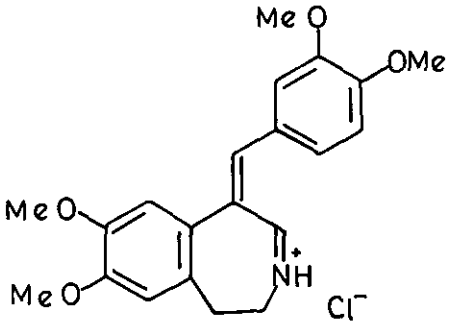

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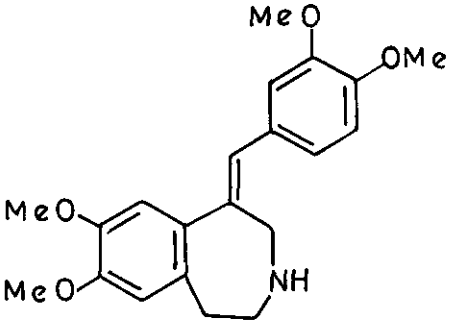

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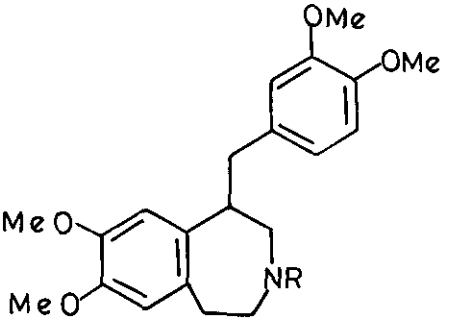
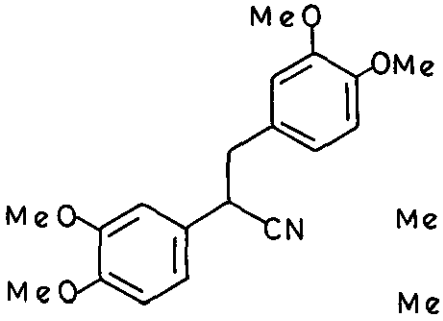
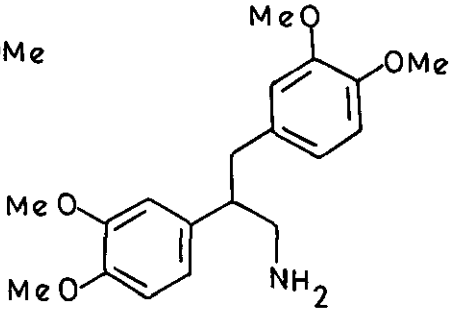


(10)

Eventually the desired compound (1; R=H) was obtained by the following route: hydrogenation of the nitrile (11)[6] over Adams' catalyst and treatment of the derived amine (12) with bromoacetaldehyde diethylacetal, gave the diethylacetal (13) which after separation from some of the dialkylated compound (14) was cyclised with hydrochloric acid to yield, after basification, 7,8-dimethoxy-1-(3,4-dimethoxybenzyl)-2,3-dihydro-1H-3-benzazepine as a colourless oil (overall yield 23%).



(11)



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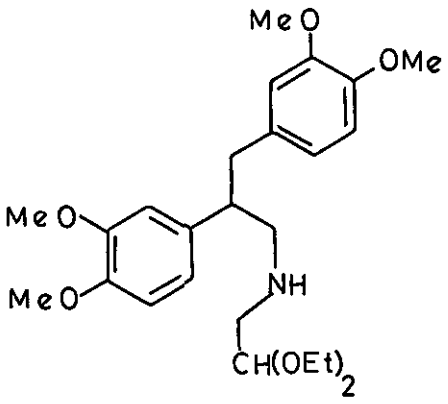

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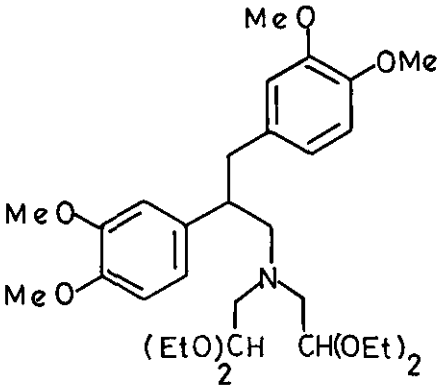

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