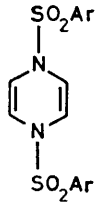
Chemistry of Reduced Pyrazines

By ULLI EISNER* and ANTHONY J. WILLIAMS
(*Department of Physical Sciences, Trent Polytechnic, Nottingham* NG1 4BU)

Summary The synthesis and reactions, including a novel isomerisation, of functionalised 1,2,3,4-tetrahydropyrazines, and their attempted conversion into 1,4-dihydropyrazines, are described.

VIRTUALLY no work has been reported on 1,2,3,4-tetrahydropyrazines. Likewise the 8π electron 1,4-dihydropyrazines have not been extensively studied and authentic derivatives of this system have become available[1] only since 1971, most of the earlier work having been shown to be erroneous.



(1)

a; Ar = Ph
b; Ar = C_6H_4Me-*p*

$ArSO_2NHCH_2CH(OR)_2$

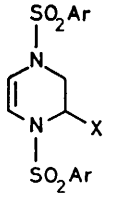
(2)

R = Me or Et

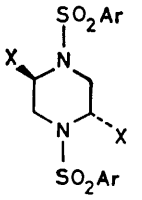
The alleged synthesis[2] of the 1,4-dihydropyrazine (**1a**) by cyclisation of the aminoacetal (**2a**) was shown by one of us[3] to lead instead to the 1,2,3,4-tetrahydropyrazine (**3a**)† or the 2,5-dihydroxypiperazine (**4a**),† according to conditions. It was found that (**4a**) was readily dehydrated to (**3a**) and that both compounds reacted with hot acidic methanol to afford (**3b**). The latter compound had been prepared earlier.[4]

This work has now been extended to the preparation of the tosyl derivatives (**3c**)† and (**4c**)† which were found to be interconvertible by the addition and elimination, respectively, of water under acid conditions. The alkoxy derivatives (**3d**,**e**)[4] and (**4d**,**e**),[4] prepared from the aminoacetal (**2b**) and the corresponding alcohol, behaved similarly. The hydroxy group in (**3c**) could be replaced by an alkoxy group to give (**3d**) and (**3e**); the reverse reaction, replacement of alkoxy by hydroxy, was also achieved. Reaction of (**3c**) with benzenethiol in acidified acetone afforded the sulphide (**3f**)† which was oxidised to the sulphoxide (**3g**)† but could not be converted into the sulphone.

Treatment of (**3c**) or (**4c**) with thionyl chloride yielded the highly insoluble (**4h**);† on brief heating in toluene this was converted into (**3h**).† The chlorine atom in the latter was very labile as expected. Thus, reaction of (**3h**) with water or ethanol gave (**3c**) and (**3e**), respectively. A number of nucleophilic substitutions were carried out on (**3h**) in aprotic solvents to afford the new compounds (**3i**—**m**).† Attempts to prepare the corresponding iodide or cyanide failed.



(3)



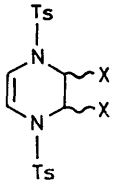
(4)

a; Ar = Ph, X = OH
b; Ar = Ph, X = OMe
c; Ar = C_6H_4Me-*p*, X = OH
d; Ar = " , X = OMe
e; Ar = " , X = OEt
f; Ar = " , X = SPh
g; Ar = " , X = SOPh
h; Ar = " , X = Cl
i; Ar = " , X = $NHCH_2Ph$
j; Ar = " , X = $NHBu^t$
k; Ar = " , X = NCS
l; Ar = " , X = SePh
m; Ar = " , X = H
n; Ar = " , X = $OCOC_6H_4Cl$

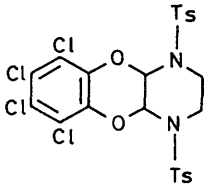
The action of bromine on (**3c**) or (**3h**) led to addition–elimination with the formation of (**5a**);† the intermediate piperazine is presumably too hindered to be isolated. Reaction of (**5a**) with water and with ethanol readily afforded (**5b**)† and (**5c**),† respectively. Treatment of (**5a**) with magnesium in dry tetrahydrofuran (THF) led to a

† Satisfactory elemental analyses and spectral data were obtained for all new compounds.

very labile isomer to which the *cis*-configuration (**5d**) was assigned. Such an isomerisation appears to be without precedent. The dibromide (**5d**) was converted into (**5e**)† and (**5f**).† The stereochemistry of the *trans*-compounds (**5a**—**c**) follows from their mode of preparation. Further evidence was provided by the fact that the *cis*-diol (**5e**), but not the *trans*-diol (**5b**), reacted[5] with $Me_2NCH(OMe)_2$, and that the chemical shift of C-2 and C-3 in the ^{13}C n.m.r. spectrum of the *trans*-compound (**5c**) was at lower field than that of the *cis*-isomer (**5f**) (*cf.*, *e.g.*, the isomeric 1,2-dichlorocyclohexanes[6]).



(5)



(6)

a; X = Br (*trans*)
b; X = OH (*trans*)
c; X = OEt (*trans*)
d; X = Br (*cis*)
e; X = OH (*cis*)
f; X = OEt (*cis*)
Ts = $MeC_6H_4SO_2$-*p*

The tetrahydropyrazines (**3**) did not undergo [4+2] cycloaddition with dienes; however, (**3m**) reacted with tetrachloro-*o*-benzoquinone to yield the novel ring system (**6**).† Oxidation of (**3c**) and (**3m**) with Jones reagent surprisingly resulted in hydroxylation of the double bond with the formation of 2,3,5-trihydroxy- and 2,3-dihydroxy-1,4-bis(*p*-toluenesulphonyl)piperazine,† respectively. All the above reactions point to the high electron density of the double bond in 1,2,3,4-tetrahydropyrazines.

Numerous attempts were made to convert (**3**) or (**5**) into the 1,4-dihydropyrazine (**1b**). Dehydration of (**3c**), dehydrohalogenation of (**3h**) or (**5d**), thermolysis of (**3g**), and debromination of (**5a**) all failed. However, reaction of (**5a**) with Zn/Cu couple in dry THF gave a highly unstable product, presumably (**1b**), which could not be isolated but which on treatment with water afforded (**3c**). Oxidation of the selenide (**3l**) with *m*-chloroperoxybenzoic acid under aprotic conditions yielded (**3n**); with aqueous hydrogen peroxide (**3l**) gave (**3c**), and with methanolic KIO_4 it afforded (**3d**). These reactions presumably proceed *via* the unstable selenoxide which fragments to (**1b**); this compound is clearly highly reactive, possibly due to its antiaromatic nature, and adds even quite weak electrophiles (*m*-$ClC_6H_4CO_2H$, H_2O, or MeOH) as soon as it is formed, giving rise to the observed products. The addition of methanol to a 1,4-dihydropyrazine has been described previously.[1a]

With one exception[7] all the known[1] 1,4-dihydropyrazines carry aryl substituents in the ring which presumably stabilise the system by alternative modes of conjugation. This may explain the failure to isolate (**1b**). Experiments to synthesise this compound are continuing.

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