Retarded Inversion of a 1*H*-Azepine Ring

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Inversion of the azepine ring in (**3**) requires a simultaneous inversion at the ring nitrogen and this accounts for the high energy barrier involved and also for the existence of stereoisomers in the case of (**6**).

From examination of the *N*-substitution of those examples of 1*H*-azepines (**1**) which are known, it appears that a strongly electron-withdrawing group on nitrogen (usually $-CO_2R$ or $-SO_2R$) enhances stability.[1] The few examples of 1*H*-azepines which lack this feature which have been reported (N–H or N–alkyl) decompose or rearrange at or below room temperature.[2,3]

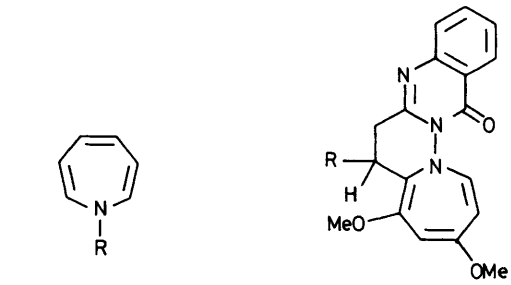
An *X*-ray crystal structure determination has shown that the *N*-*p*-bromophenylsulphonyl-1*H*-azepine (**2**) has a shallow boat shape in the crystalline state[4] and from the temperature invariance of the n.m.r. spectra down to −90 °C, it was concluded that the barrier for boat to boat inversion in 1*H*-azepines was < 5 kcal/mol.[5]†

It was at first surprising to us, therefore, to find that in the azepine (**3**) the protons within each methylene group in the reduced pyridazine ring were non-equivalent at room temperature implying that flipping of the azepine ring was slow, at least on the n.m.r. time-scale. The unexpected thermal stability of (**3**) allowed us to monitor these protons up to 140 °C (when onset of decomposition is evident) and even at this temperature their non-equivalence persists.

Examination of models or even 3-dimensional representations of (**3**) shows that the origin of this grossly inflated barrier for inversion of the azepine ring is a requirement for simultaneous inversion at the azepine nitrogen (**3a**) ⇌ (**3b**).

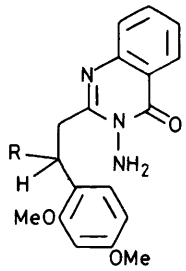
At the transition state for inversion of both the azepine nitrogen and the ring, the whole molecule, we assume, is very close to planarity. This results in an enhancement of the nitrogen inversion barrier since the lone pairs on the two adjacent nitrogens at this point are constrained to be in parallel p-orbitals. As an approximation, this inversion barrier can be equated with that required for rotation of an N–N bond in which both nitrogens are sp^2-hybridised which is known to be 19—22 kcal/mol.[6]†

We prepared (**3**) [m.p. 150—153 °C; ν_{max} (Nujol) 1677s, 1657, and 1643 cm^{-1}; ^1H n.m.r. (400 MHz; $CDCl_3$) includes δ 6.54 (d, *J* 11.5 Hz, 1H), 5.95 (dd, *J* 11.5 and 2.9 Hz, 1H), 5.52 (d, *J* 2.9 Hz, 1H), 3.69 (s, OMe), 3.54 (s, OMe), 3.19 (ddd, *J* 17, 11, and 9 Hz, 1H), 2.99 (ddd, *J* 17, 9, and 3 Hz, 1H), 2.81 (ddd, *J* 13, 9, and 3 Hz, 1H), and 2.18 (ddd, *J* 13, 11, and 9 Hz, 1H)] in 70% yield by oxidation of the *N*-aminoquinazolone (**4**), m.p. 139—140 °C, with lead tetra-acetate in chloroform. A similar oxidation of (**5**) gave the azepine (**6**) [m.p. 169—170 °C; ^1H n.m.r. ($CDCl_3$) includes δ 6.4 (d, *J* 11.7 Hz, 1H), 5.98 (dd, *J* 11.7 and 2.8 Hz, 1H), 5.42 (d, *J* 2.8 Hz, 1H), 3.36 (dd, *J* 16.5 and 7.4 Hz, 1H), 2.84 (quintet, *J* *ca.* 7 Hz, 1H), 2.59 (dd, *J* 16.5 and 0.7 Hz, 1H), and 0.90 (d, *J* 7.2 Hz, Me)] as a single stereoisomer whose assignment as (**6a**) was supported by the observation of a small nuclear Overhauser enhancement (n.O.e.) between the methyl group and the azepine ring H at δ 6.4; stereospecific formation of (**6a**) results from attack by an *N*-nitrene derived from (**5**) on the face of the aromatic ring remote from the methyl group.‡

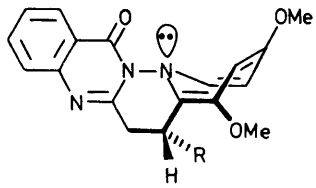


(**1**)
(**2**) R = *p*-$BrC_6H_4SO_2$

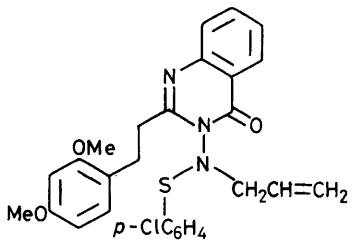
(**3**) R = H
(**6**) R = Me



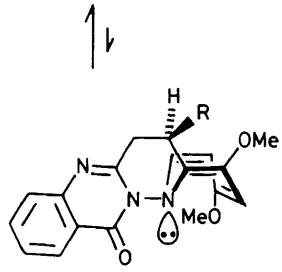
(**4**) R = H
(**5**) R = Me



(**3a**) R = H
(**6a**) R = Me



(**7**)



(**3b**) R = H
(**6b**) R = Me

When (**6a**) is warmed in chloroform, equilibration with its stereoisomer (**6b**) [^1H n.m.r. ($CDCl_3$) δ 5.95 (d, *J* 12.2 Hz, 1H), 5.85 (dd, *J* 12.2 and 2.9 Hz, 1H), 5.26 (d, *J* 2.9 Hz, 1H), 3.04 (dd, *J* 16.5 and 8.0 Hz, 1H), 2.97 (dd, *J* 16.5 and 9.8 Hz, 1H), 2.59 (m, 1H), and 1.07 (d, *J* 7.1 Hz, Me)] occurs: the ratio (**6a**):(**6b**) at equilibrium was 2:1. This equilibration however, is not first order and is presumably catalysed by adventitious acid; the slowest rate measured§ (in chlorobenzene at 135 °C) corresponds to a free energy activation barrier of *ca.* 30 kcal/mol.†

Our belief that free *N*-nitrenes are intermediates in the oxidation of (**4**) and (**5**) was supported by the isolation, in

† 1 kcal = 4.184 kJ.

‡ It is assumed that (**6a**) is formed *via* the usual benzeneimine intermediate which opens stereospecifically to (**6a**).

§ This rate of interconversion was not reliably reproducible.

good yield, of sulphenamide (**7**), when oxidation of (**4**) was carried out in the presence of allyl *p*-chlorophenyl sulphide.[7]

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