Synthesis of 3-Substituted 1,2-Benzodiazepines *via* 3*H*-1,2-Benzodiazepine *N*-Oxides

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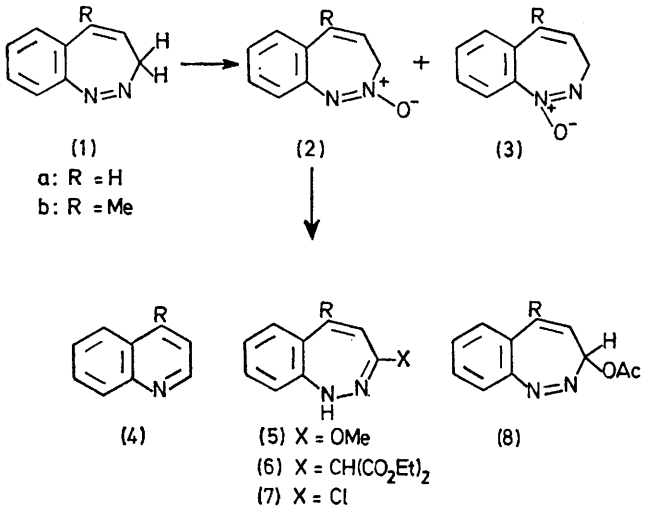
Summary Treatment of 3*H*-1,2-benzodiazepine 2-oxides (**2**), prepared from 3*H*-1,2-benzodiazepines (**1**) and *m*-chloroperbenzoic acid, with bases and acids such as alkoxides, carbanions, hydrogen chloride, and acetic acid, affords the corresponding 3-substituted 1,2-benzodiazepines (**5**)—(**8**) in moderate yields.

WE have previously reported the general synthesis of the fully unsaturated 1*H*-[1] and 3*H*-[2] 1,2-benzodiazepine, and their derivatives[3] having various substituents in all except the 3-position, by photo-induced ring expansion of *N*-iminoquinolinium ylide dimers. However, 3-substituted 1,2-benzodiazepines have not been prepared by our method because 3-substituted quinolines do not yield *N*-ylide dimers, and little is known about them. To our knowledge, only two examples have been reported; *viz.* (i) cyclopenta-1,2-benzodiazepines from β-aryl $\alpha\beta$-unsaturated ketone tosylhydrazones,[4] and (ii) 3-ethoxycarbonyl-1,2-benzodi-

azepines from phenylhydrazone hydrochlorides bearing an $\alpha\beta$-unsaturated substituent in the *ortho*-position.[5]

We now report a novel synthesis of the previously unknown title compounds (**5**)—(**8**) from 3*H*-1,2-benzodiazepines (**1**) *via* their *N*-oxides (**2**) (Scheme 1).



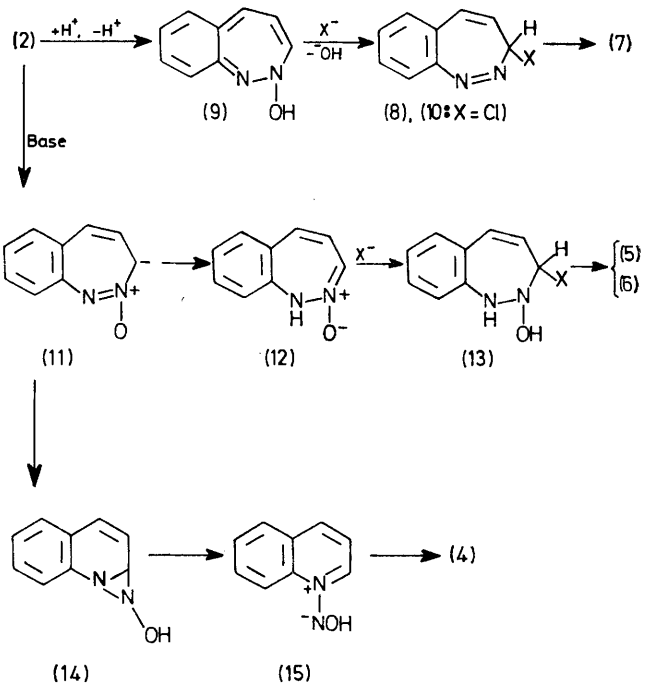
SCHEME 1

N-Oxidation of the diazepines (**1**) with *m*-chloroperbenzoic acid and chromatography over alumina gave the 2-oxides (**2**), and the 1-oxides (**3**), in yields of 60—65 and 20—22%, respectively.† The orientation of the *N*-oxide group in (**2**) and (**3**) was established by n.m.r. data.

The desired 3-substituted diazepines were obtained in moderate yields by treatment of the 2-oxides (**2**) with both bases and acids. The reaction of (**2**) with sodium methoxide in methanol gave, besides the parent quinolines (**4**), yield 20—25%, the 3-methoxy 1*H*-diazepines (**5a**), m.p. 85—86 °C, and (**5b**) m.p. 94—95 °C, in 60—70% yields.‡ Similar results were obtained when the 2-oxides (**2**) were treated with sodium ethoxide, butoxide, and benzyloxide.

As an example of the reaction with carbanions, the reaction of (**2**) with diethyl malonate in the presence of sodium methoxide gave the diazepines (**6**), as viscous oils, in yields of *ca.* 60% and the quinolines (**4**), 15—20%.

When the oxides (**2**) were treated with dry hydrogen chloride in ether, the 3-chloro-1*H*-diazepines (**7a**), m.p. 58—59 °C, and (**7b**), m.p. 86—87 °C, were obtained almost quantitatively. However, treatment with acetic acid led to the 3-acetoxy-3*H*-diazepines (**8a**), m.p. 84—85 °C, and (**8b**), m.p. 62—63 °C, yield *ca.* 50% and not their 1*H*-isomers.



SCHEME 2

A possible mechanism for the reactions is shown in Scheme 2. The acid-catalysed reaction may involve initial protonation at the *N*-oxide oxygen and subsequent elimination of a 3-hydrogen to the intermediates (**9**), followed by addition of the nucleophiles to give the 3*H*-diazepines (**8**) and (**10**). 3*H*-1,2-Benzodiazepines are known readily to undergo tautomerization to their 1*H*-isomers;[2] however, the acetoxy compounds (**8**), which were also obtained by treatment of (**1**) with lead tetra-acetate, do not tautomerize.

The base-catalysed reaction may proceed by two competing paths: (i) isomerization to the 1*H*-diazepines (**12**) *via* (**11**), followed by addition of the nucleophiles to give the diazepines (**5**) and (**6**); (ii) cyclization to the diaziridine intermediates (**14**), followed by ring-opening to give the quinolines (**4**) *via* the ylides (**15**).

(*Received*, 15*th March* 1976; *Com.* 266.)

† Structure elucidation of the *N*-oxides (**2**) and (**3**) is based on elemental analysis, and n.m.r. and mass spectra; *e.g.*, (**2a**): m.p. 85—86 °C; δ ($CDCl_3$) 4·56 (2H, br d, 3-H), 6·14 (1H, m, 4-H), 7·07 (1H, d, 5-H), and 7·2—7·6 (4H, m, Ar-H); (**3a**): m.p. 93—94 °C; δ ($CDCl_3$) 3·94 (2H, br d, 3-H), 6·65 (1H, m, 4-H), 6·84 (1H, d, 5-H), and 7·2—7·6 (3H, m, Ar-H), and 8·03 (1H, m, 9-H).

‡ New benzodiazepines obtained were characterized by elemental analysis and i.r., n.m.r., and mass spectroscopy, and by spectral comparison with the 1,2-benzodiazepines already reported.[1-3]

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[5] L. Garanti, A. Scandroglio, and G. Zecchi, *Tetrahedron Letters*, 1975, 3349.