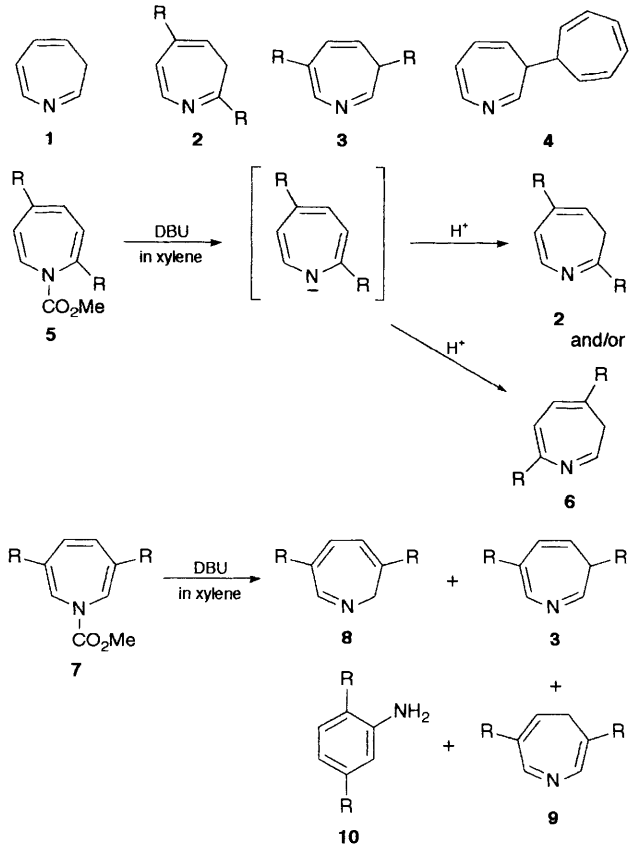
Synthesis and Characterization of 2*H*-, 3*H*- and 4*H*-Azepine: The First Observation of the Thermal Distribution Equilibrium of Azepines

Kyosuke Satake,* Ryoichi Okuda, Michiaki Hashimoto, Yasushi Fujiwara, Izumi Watadani, Hideki Okamoto, Masaru Kimura and Shiro Morosawa

Department of Chemistry, Faculty of Science, Okayama University, Tsushima Naka 3-1-1, Okayama, 700 Japan

Demethoxycarbonylation of methyl 2,5,-di-*tert*-butyl-1*H*-azepine-1-carboxylate using 1,8-diazabicyclo[5.4.0]undec-7-ene gives exclusively two isomers of 3*H*-azepine derivatives, while methyl 3,6-di-*tert*-butyl-1*H*-azepine-1-carboxylate gives a mixture of 2*H*-, 3*H*- and 4*H*-azepine derivatives under the same conditions because of a 1,5-hydrogen shift in the resulting triene system.

The general synthetic method for 3*H*-azepine derivatives is based on the intramolecular insertion reaction of phenylnitrene in nucleophilic media.[1] The direct conversion of methyl 1*H*-azepine-1-carboxylate to the labile 3*H*-azepine **1** was accomplished by Vogel *et al.* using iodotrimethylsilane as a demethoxycarbonylating agent.[2] Previously, we have reported the indirect conversion of methyl 2,5- and 3,6-di-*tert*-butyl-1*H*-azepines to the corresponding alkylated 3*H*-azepines, **2** and **3**, *via* 3a,5a-dihydro-1*H*-cyclobuta[*b*]pyrrole derivatives.[3] Nitta *et al.* have also reported the synthesis of 3-(2,4,6-cycloheptatrienyl)-3*H*-azepine **4** *via* an iron carbonyl complex of 1*H*-azepine-1-carboxylate.[4] We now report the direct synthesis of 3*H*-azepines from methyl 2,5- and methyl 3,6-di-*tert*-butyl-1*H*-azepine-1-carboxylate (**5** and **7**)[5] by means of demethoxycarbonylation using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The latter gives not only



Scheme 1 R = Bu^t

3*H*-azepine derivative **3** but also 2*H*- and 4*H*-azepine derivatives **8** and **9** simultaneously which were thought to be thermodynamically less stable compared with the 3*H*-azepine system (Scheme 1).

A representative procedure for the demethoxycarbonylation reaction of di-*tert*-butyl-1*H*-azepine derivatives **5** and **7** was as follows. A solution of methyl 2,5-di-*tert*-butyl-1*H*-azepine-1-carboxylate **5** (2.0 g, 7.6 mmol) and DBU (12 g, 78 mmol) in dry xylene (12 ml) was refluxed under a nitrogen stream for 6 h. After cooling, the reaction mixture was introduced into a silica-gel column and eluted with ethyl acetate : hexane (1 : 4 v/v) in order to eliminate the excess of DBU and the polymeric compounds formed. From this eluent, 2,5- and 4,7-di-*tert*-butyl-3*H*-azepines **2** and **6** were obtained by preparative medium pressure liquid chromatography (MPLC) using a silica gel column (Woelm 32–63) in 54 and 22% yield, respectively. On the other hand, methyl 3,6-di-*tert*-butyl-1*H*-azepine-1-carboxylate **7** gave 3,6-di-*tert*-butyl substituted 2*H*-azepine **8**, 3*H*-azepine **3**, 4*H*-azepine **9** and 2,5-di-*tert*-butylaniline **10** under the same conditions in 11, 46, 1.3 and 8.3% yield, respectively. Compounds **2** and **3** were identical with the previously reported 3*H*-azepines in all respects, respectively. The new isomer **6** of 3*H*-azepine **2** was readily characterized by comparing the values of the coupling constants of the AB-quartet ($J_{5,6}$ 6.7 Hz) and their chemical shifts ($\delta_{H\text{-}5}$ 6.14 and $\delta_{H\text{-}6}$ 6.06) with those of **2** ($J_{6,7}$ 8.5 Hz, $\delta_{H\text{-}6}$ 6.28 and $\delta_{H\text{-}7}$ 7.28). The structure of 3,6-di-*tert*-butyl-2*H*- and 3,6-di-*tert*-butyl-4*H*-azepines **8** and **9** were also elucidated by reference to the ^{1}H and ^{13}C NMR spectra of previously obtained 3*H*-azepines **2** or **3**. Assignment for all the azepines of their ^{1}H and ^{13}C NMR spectra, which are summarized in Table 1 for proton and Table 2 for carbon, were performed on the basis of ^{1}H-COSY and ^{1}H–^{13}C correlation (HETCOR) measurements.

When *N*-ethoxycarbonyl derivatives were used as starting materials instead of **5** or **7**, the above reaction did not occur and there was a complete recovery of the starting materials. It is considered, in the case of *N*-methoxycarbonyl derivatives **5** and **7**, that the reaction initially promotes an effective demethylation of the methoxycarbonyl group by a strong base (DBU)[6] followed by decarboxylation to give the 3*H*-azepine systems.

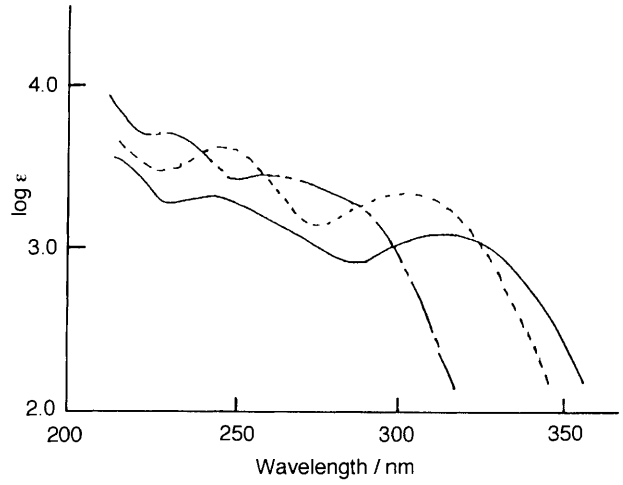


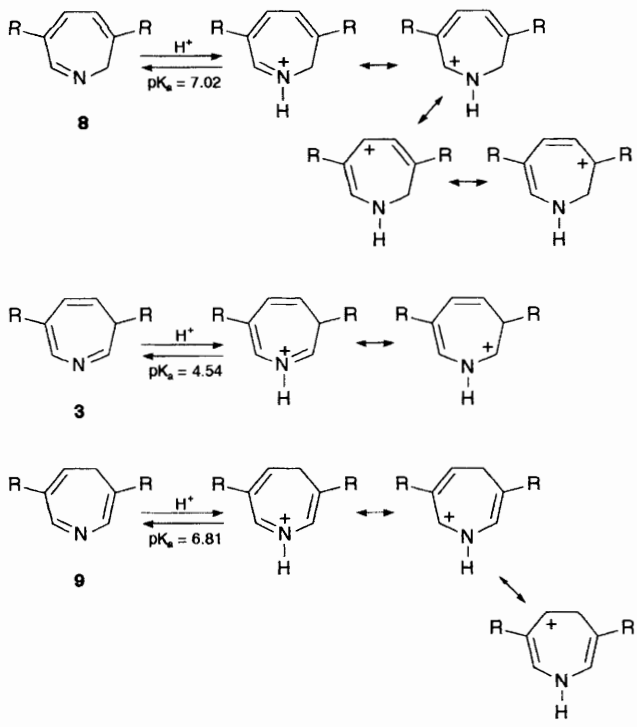
Fig. 1 Electronic spectra of 2*H*-, 3*H*- and 4*H*-azepine derivatives **8** (——), **3** (—·—) and **9** (– – –) in ethanol

Table 1 ^{1}H NMR data (500 MHz; $CDCl_3$) for the ring protons of azepines **8**, **2**, **3**, **6** and **9**

	δ						
Compound	H-2	H-3	H-4	H-5	H-6	H-7	*J*/Hz
2*H*-type							
8	3.5	—	6.09	6.60	—	7.91	$J_{4,5}$ 6.2 $J_{5,7}$ 1.9
3*H*-type							
2	—	1.1 3.6	5.03	—	6.28	7.28	$J_{3,4}$ 7.0 $J_{6,7}$ 8.5
3	6.46	0.79	5.17	6.43	—	7.44	$J_{2,3}$ 4.8 $J_{3,4}$ 5.9 $J_{3,5}$ 1.7 $J_{4,5}$ 9.4 $J_{5,7}$ 1.9
6	6.50	1.1 3.6	—	6.14	6.06	—	$J_{2,3}$ 5.0 $J_{5,6}$ 6.7
4*H*-type							
9	6.73	—	2.05	5.54	—	8.55	$J_{4,5}$ 7.3 $J_{5,7}$ 2.1

Table 2 ^{13}C NMR data (125 MHz; $CDCl_3$) for the ring carbons of azepines **8**, **2**, **3**, **6** and **9**

	δ					
Compound	H-2	H-3	H-4	H-5	H-6	H-7
2*H*-type						
8	52.2	150.6	119.1	128.6	151.0	158.7
3*H*-type						
2	164.0	32.4	110.0	147.3	115.9	139.7
3	139.6	54.3	116.5	125.5	139.0	135.4
6	136.4	35.1	136.8	118.6	108.9	160.1
4*H*-type						
9	130.7	140.9	26.4	125.6	142.8	160.1



Scheme 2 R = Bu^t

Recently, the first example of a 1,5-hydrogen shift in the 3*H*-azepine system has been reported concerning compound **4**.[4] At a glance, the reason for the simultaneous formation of compounds **2** and **6** is considered to be a 1,5-hydrogen shift between these two. The possibility of a 1,5-hydrogen shift between 3*H*-azepines **2** and **6** was examined next from both sides. Under the demethoxycarbonylation conditions, neither **2** nor **6** gave the complementary isomers **6** and **2**, respectively. This indicates that the simultaneous formation of the 3*H*-azepine isomers may be the result of competitive prototropy of the intermediary 1*H*-azepine or its anion under the demethoxycarbonylation conditions. On the other hand, on heating at 125 °C in toluene for 5 h, 2*H*- or 3*H*-azepine converted quantitatively into an azepine mixture consisting of 2*H*-, 3*H*- and 4*H*-azepines **8**, **3** and **9** (12:51:1 from 2*H*-azepine **8** or 12:56:1 from 3*H*-azepine **3**). This result shows that the distribution of azepine isomers is proportional to the thermal stability of the seven-membered triene system owing to the thermally allowed 1,5-hydrogen shift.

The electronic spectra in ethanol of 2*H*-, 3*H*- and 4*H*-azepines **8**, **3** and **9** are shown in Fig. 1. These show a dependence on the pH of the medium owing to the basic nitrogen in the system. The basic character of these sp^2-nitrogen atoms incorporated into the triene systems were estimated by a spectroscopic method. The pK_a values for the conjugated acids of **8**, **3** and **9** were determined as 7.02, 4.54 and 6.81, respectively, on the basis of pH dependent spectra in a buffer solution. The terminal sp^2-nitrogen shows stronger basic character than the others. It seems reasonable to assume that the stability of the conjugated acid is influenced by resonance stabilization of the system (Scheme 2).

We thank the SC-NMR Laboratory of Okayama University for the 500 MHz ^{1}H and 125 MHz ^{13}C NMR measurements.

Received, 8th May 1991; Com 1/02175C

References

1 R. Huisgen and M. Appl, *Chem. Ber.*, 1958, **91**, 1; R. J. Sundberg, S. R. Suter and M. Brenner, *J. Am. Chem. Soc.*, 1972, **94**, 513; M. Masaki, K. Fukui and J. Kita, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2013; R. Purvis, R. K. Smalley, W. A. Strachan and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1978, 191; R. Purvis, R. K. Smalley, H. Suschitzky and M. A. Alkhader, *J. Chem. Soc., Perkin Trans. 1*, 1984, 249.

2 E. Vogel, H.-J. Altenbach, J.-M. Drossard, H. Schmickler and H. Stegelmeier, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 1016.

3 K. Satake, H. Saitoh, M. Kimura and S. Morosawa, *J. Chem. Soc., Chem. Commun.*, 1988, 1121.

4 M. Nitta, K. Shibata and H. Miyano, *Heterocycles*, 1989, **29**, 253.

5 T. Kumagai, K. Satake, K. Kidoura and T. Mukai, *Tetrahedron Lett.*, 1983, **24**, 2275; K. Satake, T. Kumagai and T. Mukai, *Chem. Lett.*, 1983, 743; K. Satake, T. Kumagai and T. Mukai, *Chem. Lett.*, 1984, 2033; T. Kumagai, S. Tanaka and T. Mukai, *Tetrahedron Lett.*, 1984, **25**, 5569.

6 E. J. Parish and D. M. Miles, *J. Org. Chem.*, 1973, **38**, 1223.