

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

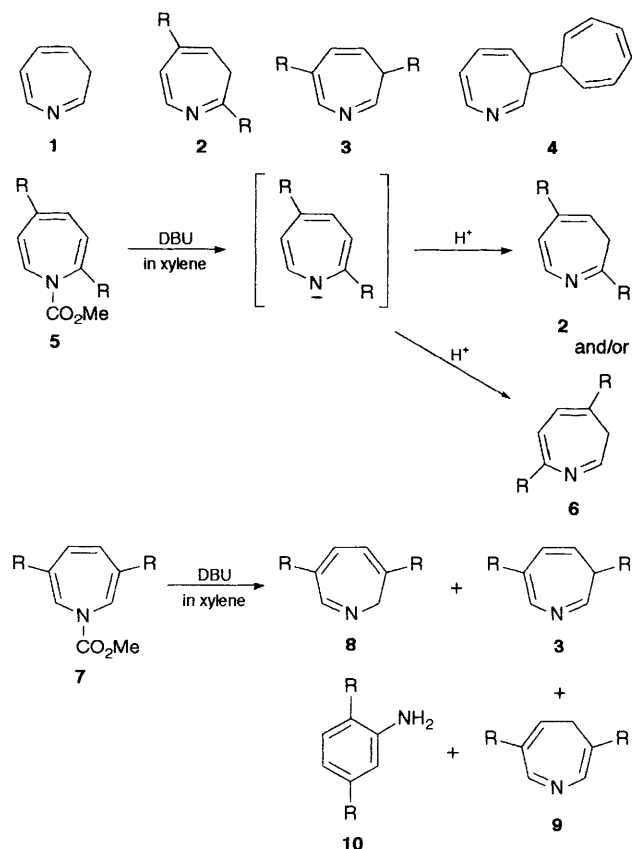
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Demethoxycarbonylation of methyl 2,5-di-*tert*-butyl-1*H*-azepine-1-carboxylate using 1,8-diazabicyclo[5.4.0]undec-7-ene gives exclusively two isomers of 3*H*-azepine derivatives, while methyl 3,6-di-*tert*-butyl-1*H*-azepine-1-carboxylate gives a 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 phenyl-nitrene in nucleophilic media.<sup>1</sup> 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.<sup>2</sup> 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*-aze-

pines, **2** and **3**, via 3a,5a-dihydro-1*H*-cyclobuta[*b*]pyrrole derivatives.<sup>3</sup> 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.<sup>4</sup> 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**)<sup>5</sup> by means of demethoxycarbonylation using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The latter gives not only

Scheme 1 R = Bu<sup>t</sup>

*3H*-azepine derivative **3** but also *2H*- and *4H*-azepine derivatives **8** and **9** simultaneously which were thought to be thermodynamically less stable compared with the *3H*-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-*3H*-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 *2H*-azepine **8**, *3H*-azepine **3**, *4H*-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 *3H*-azepines in all respects, respectively. The new isomer **6** of *3H*-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 ( $\delta_{H-5}$  6.14 and  $\delta_{H-6}$  6.06) with those of **2** ( $J_{6,7}$  8.5 Hz,  $\delta_{H-6}$  6.28 and  $\delta_{H-7}$  7.28). The structure of 3,6-di-*tert*-butyl-*2H*- and 3,6-di-*tert*-butyl-*4H*-azepines **8** and **9** were also elucidated by reference to the  $^1H$  and  $^{13}C$  NMR spectra of previously obtained *3H*-azepines **2** or **3**. Assignment for all the azepines of their  $^1H$  and  $^{13}C$  NMR spectra, which are summarized in Table 1 for proton and Table 2 for carbon, were performed on the basis of  $^1H$ -COSY and  $^1H$ - $^{13}C$  correlation (HETCOR) measurements.

When *N*-ethoxycarbonyl derivatives were used as starting materials instead of **5** or **7**, the above reaction did not occur

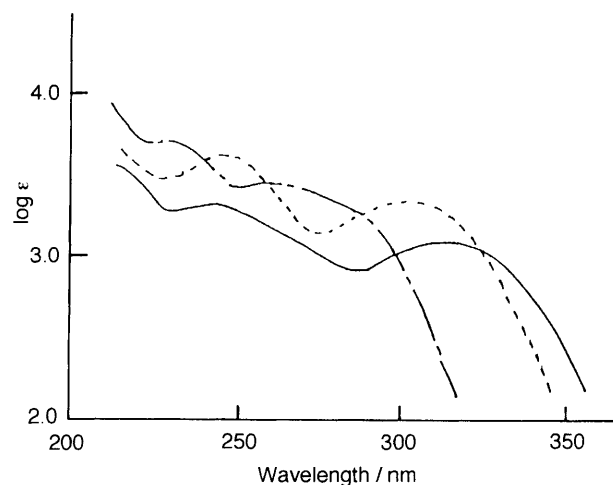


Fig. 1 Electronic spectra of *2H*-, *3H*- and *4H*-azepine derivatives **8** (—), **3** (---) and **9** (- - -) in ethanol

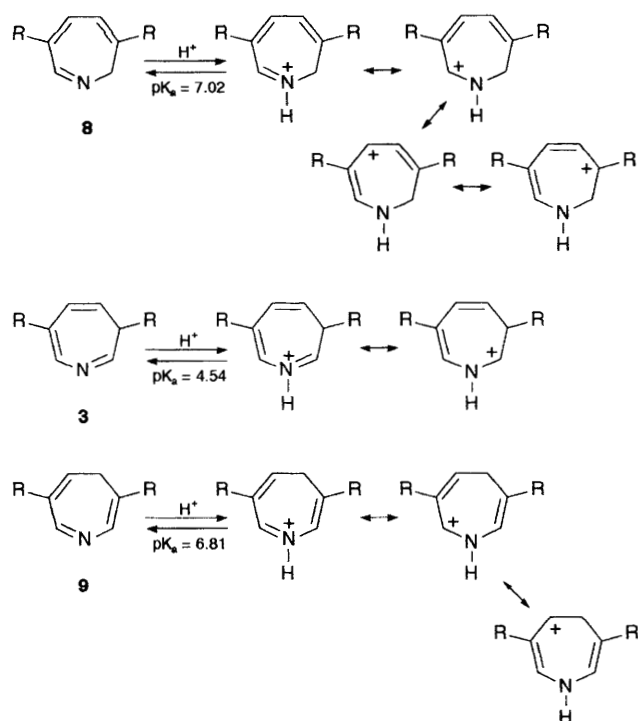
Table 1  $^1H$  NMR data (500 MHz;  $CDCl_3$ ) for the ring protons of azepines **8**, **2**, **3**, **6** and **9**

Compound	$\delta$						$J$ /Hz
	H-2	H-3	H-4	H-5	H-6	H-7	
<i>2H</i> -type <b>8</b>	3.5	—	6.09	6.60	—	7.91	$J_{4,5}$ 6.2 $J_{5,7}$ 1.9
<i>3H</i> -type <b>2</b>	—	1.1 3.6	5.03	—	6.28	7.28	$J_{3,4}$ 7.0 $J_{6,7}$ 8.5 $J_{2,3}$ 4.8 $J_{3,5}$ 5.9
<b>3</b>	6.46	0.79	5.17	6.43	—	7.44	$J_{3,5}$ 1.7 $J_{4,5}$ 9.4 $J_{5,7}$ 1.9
<b>6</b>	6.50	1.1 3.6	—	6.14	6.06	—	$J_{2,3}$ 5.0 $J_{5,6}$ 6.7
<i>4H</i> -type <b>9</b>	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**

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

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)<sup>6</sup> followed by decarboxylation to give the *3H*-azepine systems.

Scheme 2 R = Bu<sup>t</sup>

Recently, the first example of a 1,5-hydrogen shift in the 3*H*-azepine system has been reported concerning compound **4**.<sup>4</sup> 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<sup>2</sup>-nitrogen atoms incorporated into the triene systems were estimated by a spectroscopic method. The p*K*<sub>a</sub> 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<sup>2</sup>-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).

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