An Alternative Synthetic Route to 3*H*-Azepines: Thermal Isomerization of 2,4- and 3,5-Di-t-butyl-3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrroles

Kyosuke Satake,* Hidekazu Saitoh, Masaru Kimura, and Shiro Morosawa

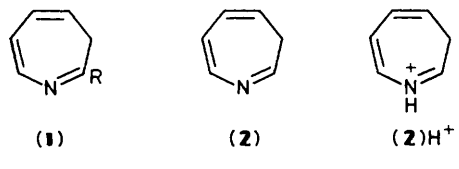
Department of Chemistry, Faculty of Science, Okayama University, Tsushima-Naka 3-1-1, Okayama 700, Japan

Di-t-butyl derivatives of 3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrroles, synthesized from photoisomers of 1*H*-azepine derivatives (Dewar azepines), isomerized thermally to 3*H*-azepines.

The intramolecular insertion reaction of phenylnitrene in nucleophilic media has been considered a general synthetic method for 3*H*-azepine derivatives (**1**).[1] The resulting 3*H*-azepines, however, possess necessarily a strongly electron-donating functional group on the ring which may hinder study of the 3*H*-azepine system *per se*.

Recently, Vogel reported the formation of 3*H*-azepine (**2**) from methyl 1*H*-azepine-1-carboxylate under fairly sophisticated conditions.[2] We report here an alternative route to 3*H*-azepines from methyl 1*H*-azepine-1-carboxylate derivatives *via* thermal isomerization of 3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrrole derivatives.

The Dewar azepines (**4a** and **b**) (methyl 3,5- and 2,4-di-t-butyl-3a,5a-dihydro-1*H*-cyclobuta[*b*]pyrrole-1-carboxylates)† were obtained by irradiation of the corresponding 1*H*-azepine derivatives (**3a** and **b**)[3] in methanol with a 450 W high-pressure mercury lamp through a Pyrex filter, in 87 and 81% yields, respectively.[4] The products were demethoxycarbonylated in butanol with potassium hydroxide as follows. When a butanolic solution of an equimolar mixture of potassium hydroxide and the Dewar azepine (**4a** or **b**) was heated for 15 min at 120 °C, carbon dioxide was liberated. When the reaction was complete, the butanol was evaporated off. 3,5-Di-t-butyl-3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrrole (**5a**)‡ was obtained from the ethereal extract of the neutralized reaction mixture with dilute hydrochloric acid as colourless prisms (m.p. 46—47 °C), in 42% yield. 2,4-Di-t-butyl-3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrrole (**5b**) was isolated as a pale yellow oil in 45% yield by extraction with ether of the alkaline reaction mixture diluted with water. The difference in extractability of (**5a**) and (**5b**) suggests a greater acidity of the C-3 proton of (**5a**) than of (**5b**). On the basis of the Karplus equation[5] for the torsion angles of vicinal protons, the observed coupling constant (3.3 Hz) between the C-3 and C-3a protons in (**5a**) supports the view that the t-butyl group and the C-3a proton are *cis*-oriented. Accordingly, the corresponding anion (**8**) may be stabilized because of the avoidance of steric repulsion between the large t-butyl group and the *cis*-vicinal C-3a proton. The energy of stabilization appears to be an important factor in increasing the acidity of the C-3 proton. The structures of these compounds were further confirmed as imines by i.r. spectra ($\nu_{max.}$ 1605 and 1615 cm^{-1}; N=C stretching), and by the presence of three kinds of sp^2 carbon signal in both ^{13}C n.m.r. spectra.



When a benzene solution (3.66×10^{-2} mol l^{-1}) of the imine (**5a**) or (**5b**) was heated for 12 h at 120 °C in a sealed glass tube, ring opening occurred to give 3,6-di-t-butyl-3*H*-azepine (**6a**) as pale yellow crystals (m.p. 26—27 °C) in 85% yield, or 2,5-di-t-butyl-3*H*-azepine (**6b**) as a pale yellow oil in 55% yield. A kinetic study of the thermal isomerization of (**5a**) and (**5b**) was carried out at 130 °C by peak area measurement in ^1H n.m.r. (C_6D_6). Good first-order plots were obtained in both cases and the reaction rates were determined as $3.06 \pm 0.11 \times 10^{-4}$ s^{-1} for (**5a**) and $4.46 \pm 0.07 \times 10^{-5}$ s^{-1} for (**5b**). The electronic spectra of (**6a**) and (**6b**), together with that of the isoelectronic cycloheptatriene, are shown in Figure 1.

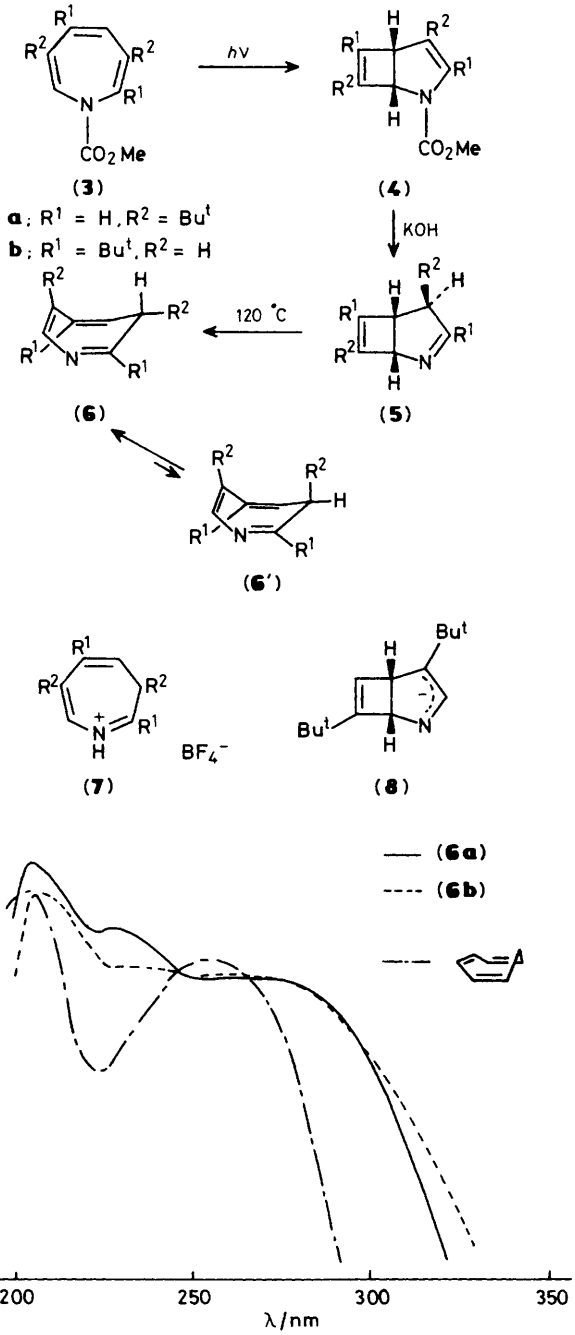


Figure 1. Electronic spectra of 3*H*-azepine derivatives (**6a** and **b**) and cycloheptatriene in ethanol.

† All new compounds described here gave satisfactory spectroscopic and analytical data.

‡ *Spectral data* for (**5a**): i.r. (Nujol; cm^{-1}) 1605; δ_H (500 MHz; $CDCl_3$) 0.89 (s, 9H), 1.04 (s, 9H), 2.27 (dd, *J* 3.3 and 2.5 Hz, 1H), 2.69 (t, *J* 3.3 Hz, 1H), 4.91 (m, 1H), 5.72 (s, 1H), and 7.43 (s, 1H); δ_C (22.5 MHz; $CDCl_3$) 27.7 (q), 28.2 (q), 33.1 (s), 40.0 (d), 62.1 (d), 78.5 (d), 128.1 (d), 168.3 (s), and 168.6 (d); u.v. (EtOH; nm) 255 (log ε 2.44).

For (**5b**): i.r. (neat; cm^{-1}) 1615; δ_H (500 MHz; $CDCl_3$) 1.02 (s, 9H), 1.10 (s, 9H), 2.49 (ddd, *J* 18.0, 10.2, and 2.0 Hz, 1H), 2.57 (dt, *J* 18.0 and 3.5 Hz, 1H), 3.20 (dtd, *J* 10.2, 3.5, and 1.2 Hz, 1H), 4.71 (m, 1H), and 6.05 (s, 1H); δ_C (22.5 MHz; $CDCl_3$) 28.0 (q), 28.4 (q), 33.5 (s), 34.8 (t), 35.9 (s), 42.1 (d), 74.4 (d), 132.2 (d), 162.8 (s), and 183.7 (s); u.v. (EtOH; nm) 222.5 (sh) (log ε 2.87).

For (**6a**): i.r (Nujol; cm^{-1}) 1585; δ_H (500 MHz; $CDCl_3$) 0.79 (ddd, *J* 5.4, 4.8, and 1.7, 1H), 1.10 (s, 9H), 1.21 (s, 9H), 5.18 (dd, *J* 9.6 and 5.4 Hz, 1H), 6.43 (dt, *J* 9.6 and 1.7 Hz, 1H), 6.46 (d, *J* 4.8 Hz, 1H), and 7.43 (d, *J* 1.7 Hz, 1H); *m/z* 205 (M^+, 18%), 190 (48), and 148 (100).

For (**6b**): i.r. (neat; cm^{-1}) 1600; δ_H (500 MHz; $CDCl_3$) 1.07 (s, 9H), 1.10 (br., 1H), 1.14 (s, 9H), 3.57 (br., 2H), 5.03 (t, *J* 7.0 Hz, 1H), 6.28 (d, *J* 8.2 Hz, 1H), and 7.29 (d, *J* 8.2 Hz, 1H); *m/z* 205 (M^+, 54%), 190 (57), 163 (81), and 107 (100).

For (**7a**): i.r. (Nujol; cm^{-1}) 3230 and 1620; δ_H (500 MHz; $CDCl_3$) 1.16 (s, 9H), 1.28 (s, 9H), 1.29 (dd, *J* 6.4 and 5.4 Hz, 1H), 5.42 (dd, *J* 9.3 and 5.4 Hz, 1H), 6.85 (d, *J* 9.3 Hz, 1H), 7.32 (s, 1H), 7.47 (d, *J* 6.4 Hz, 1H), and 12.29 (br., 1H).

For (**7b**): i.r. (Nujol; cm^{-1}) 3200 and 1650; δ_H (500 MHz; $CDCl_3$) 1.13 (s, 9H), 2.5—4.0 (br., 2H), 5.29 (t, *J* 5.5 Hz, 1H), 7.15 (d, *J* 9.5 Hz, 1H), and 7.30 (d, *J* 9.5 Hz, 1H) (N^+ *H* not apparent).

Table 1. Assigned ^{13}C n.m.r. data (125 MHz; $CDCl_3$; δ values) of ring carbon atoms for (**6a**), (**6b**), (**7a**), and (**7b**), and shift deviations (Δδ) between non-protonated and protonated species.

Position	(**6a**)	(**7a**)	Δδ	(**6b**)	(**7b**)	Δδ
2	135.6(d)	151.5(d)	+15.9	163.5(s)	182.5(s)	+19.0
3	54.5(d)	51.8(d)	−2.7	32.4(d)	31.2(t)	−1.2
4	116.3(d)	119.0(d)	+2.7	109.9(d)	114.5(d)	+4.6
5	125.5(d)	130.2(d)	+4.7	147.4(s)	152.0(s)	+4.6
6	138.8(s)	155.1(s)	+16.3	115.7(d)	130.0(d)	+14.3
7	139.1(d)	124.1(d)	−15.0	140.0(d)	127.2(d)	−12.8

Table 2. Formal charge densities of 3*H*-azepine (**2**) and its protonated derivative (**2**) H^+ calculated by MNDO.

Position	1	2	3	4	5	6	7
(**2**)	−0.245	+0.079	+0.020	−0.105	−0.037	−0.107	+0.038
(**2**)H^+	−0.092	+0.240	−0.004	−0.056	−0.070	+0.050	−0.048
(**2**)H^+ − (**2**)	+0.153	+0.161	−0.024	+0.049	−0.033	+0.157	−0.086

^{13}C N.m.r. spectra of both (**6a**) and (**6b**) showed that the system contains five kinds of sp^2 carbon (see Table 1). The presence of isomers (*e.g.* 1*H*-azepine or azanorcaradiene) was excluded by both ^1H and ^{13}C n.m.r. spectra. The C-3 proton signals of (**6b**) appeared at δ 1.10 and 3.57, each as a slightly broadened peak, and that of (**6a**) appeared as a sharp triple doublet peak at δ 0.79 at 25 °C. The corresponding protons of (**2**) resonated at δ *ca.* 2.3.[2] Steric hindrance due to the two t-butyl groups on the ring may raise the activation energy for the ring inversion [(**6**) ⇌ (**6′**)]. The 3*H*-azepines (**6a** and **b**) gave protonated species (**7a** and **b**) as colourless prisms [m.p. 114 and 145 °C (decomp.), respectively] in quantitative yield, when treated with hydrogen tetrafluoroborate in acetonitrile. The ^{13}C n.m.r. chemical shifts of (**6a**), (**6b**), (**7a**), and (**7b**) were assigned by means of heteronuclear (^{13}C–^1H) *J*-correlated two-dimensional n.m.r. (HETCOR) and are listed in Table 1, along with incremental or decremental protonation values (Δδ). The Δδ values for (**6a**)/(**7a**) and (**6b**)/(**7b**) showed a fairly good correlation. These assignments were in accord with the result of theoretical calculations of formal charge densities for the 3*H*-azepine (**2**) and its protonated derivative (**2**)H^+ by MNDO (Table 2).[6] Differences in calculated formal charges between (**2**) and (**2**) H^+ are similar to the Δδ values, especially at C-2, C-6, and C-7.

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

Received, 29th March 1988; Com. 8/01274A

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