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Studies on Diazepines. XXIII.[1] Reactions of Monocyclic 1*H*-1,3-Diazepines. (1). Cycloaddition Reaction with 2,5-Dimethyl-3,4-diphenylcyclopentadienone

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The thermal cycloaddition reaction of 1-ethoxycarbonyl-1*H*-1,3-diazepines (**4a**, **b**) with 2,5-dimethyl-3,4-diphenylcyclopentadienone (**5**) gave three kinds of 1 : 1 cycloadducts, *exo* [6+4]π (**6**), *syn-endo* [4+2]π (**7**), and *anti-endo* [4+2]π (**8**) cycloadducts, the structures of which were elucidated by spectral analyses and the following photochemical study. Irradiation of the [4+2]π cycloadducts **7** and **8** resulted in an intramolecular [2+2]π cycloaddition to afford the cage compounds **12** and **13**, respectively, while the [6+4]π cycloadducts (**6**), upon irradiation, underwent a retro-reaction to give the bicyclic compounds (**11**), presumably *via* the parent 1,3-diazepines (**4**).

Keywords——thermal cycloaddition; 1*H*-1,3-diazepine; cyclopentadienone; [6+4]π cycloadduct; [4+2]π cycloadduct; cage compound; IR; NMR

The cycloaddition reactions of fully unsaturated seven-membered heterocyclic compounds[2] such as oxepines,[3] 1*H*-azepines,[4,5] 1*H*-1,2-diazepines,[6] and 1,3-oxazepines[7] with a variety of dienophiles and dienes have been extensively studied, because these compounds possess many reaction sites and thus can undergo intermolecular cycloadditions as monoenes, dienes, or trienes, in addition to norcaradiene forms. It has been reported[7] that although the 1,3-oxazepine (**1**) did not add to dienophiles such as maleic anhydride, *N*-phenylmaleimide, and dimethyl acetylenedicarboxylate, it reacted with 2,5-dimethyl-3,4-diphenylcyclopentadienone. Some interesting results of cycloadditions of the 1*H*-azepine (**2**)[5] and the 1*H*-1,2-diazepine (**3**)[7] to cyclopentadienones have also been reported. In connection with these results, we examined such reactions of the 1*H*-1,3-diazepines (**4**), which are new heterocycles recently prepared by us[8] and are considered to have more electron-deficient triene systems than those of the oxazepine (**1**) and the azepine (**2**). We report here the results of the cycloaddition reaction of **4** with 2,4-dimethyl-3,4-diphenylcyclopentadienone (**5**).

1 **2** **3** **4**

Chart 1

Heating a mixture of ethyl 5-methyl-1*H*-1,3-diazepine-1-carboxylate (**4a**) and the cyclopentadienone (**5**)[9] in refluxing xylene (at *ca.* 140 °C) for 6 d resulted in the formation of three crystalline products, **6a** (mp 140—142 °C, 7%), **7a** (mp 188—190 °C, 26%), and **8a** (mp 157—159 °C, 31%). The 1,3-diazepine (**4b**) having an electron-donating methoxy group also reacted with **5** to give three products, **6b** (mp 165—168 °C, 30%), **7b** (mp 195—197 °C, 18%), and **8b** (mp 230—232 °C, 12%) on heating for 3 d under similar conditions.

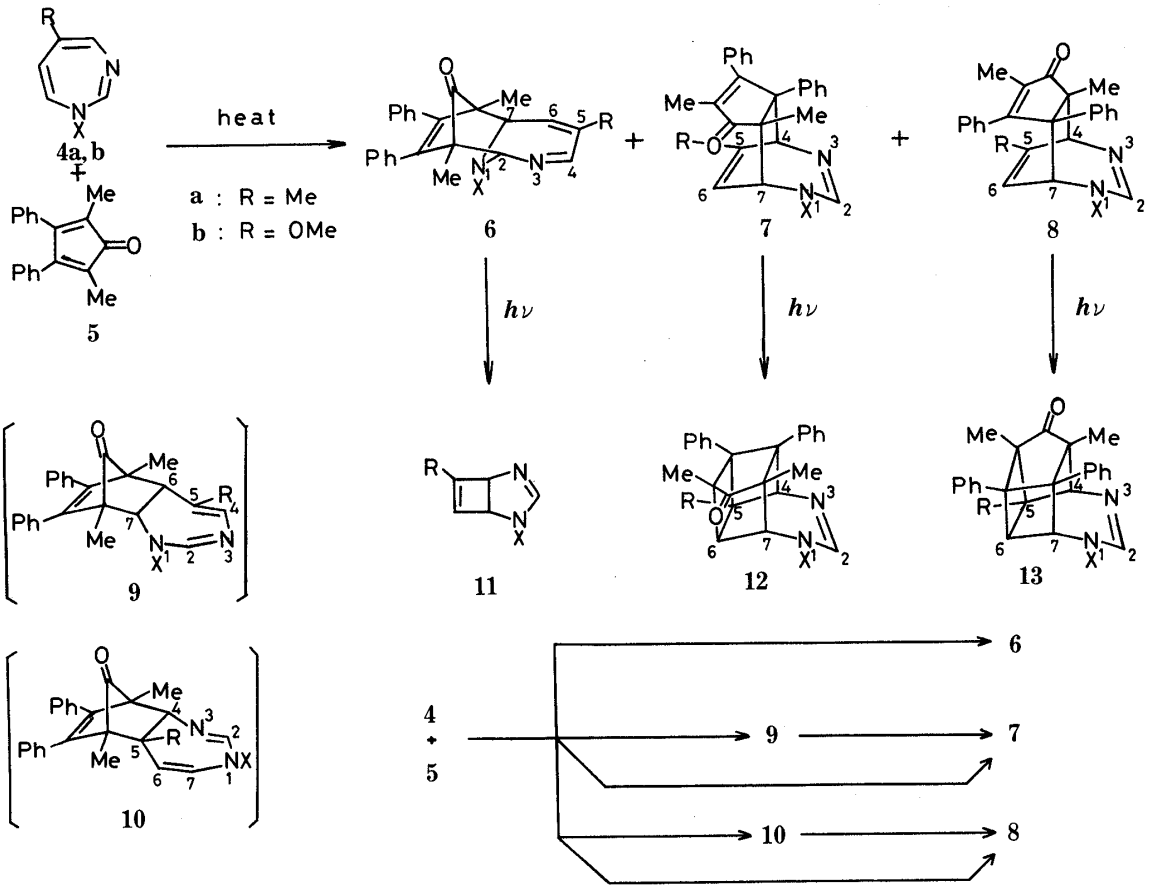

Chart 2

TABLE I. The Cycloadducts (**6**, **7**, and **8**) and the Cage Compounds (**12** and **13**)

Compd. No.	Yield[a] (%)	mp (°C)	IR ν_{max} cm^{-1} (C=O)	Formula (MS *m/z*: M$^+$)	Analysis (%) Calcd (Found) C	H	N
6a	7	140—142[b]	1760	$C_{28}H_{28}N_2O_3$	76.34	6.41	6.36
			1690	(440)	(76.60	6.31	6.23)
6b	30	166—168[b]	1760	$C_{28}H_{28}N_2O_4$	73.66	6.18	6.14
			1690	(456)	(73.89	6.12	5.96)
7a	26	188—190[b]	1720	$C_{28}H_{28}N_2O_3$	76.34	6.41	6.36
			1690	(440)	(76.43	6.63	6.30)
7b	18	194—197[b]	1715	$C_{28}H_{28}N_2O_4$	73.66	6.18	6.14
			1690	(456)	(73.58	6.22	5.98)
8a	31	157—159[b]	1720	$C_{28}H_{28}N_2O_3$	76.34	6.41	6.36
			1690	(440)	(76.21	6.36	6.33)
8b	12	230—232[b]	1720	$C_{28}H_{28}N_2O_4$	73.66	6.18	6.14
			1690	(456)	(73.77	6.09	6.01)
12	86	199—201[c]	1760	$C_{28}H_{28}N_2O_3$	76.34	6.41	6.36
			1720	(440)	(76.28	6.30	6.34)
			1660 (C=N)				
13	91	214—217[d]	1760	$C_{28}H_{28}N_2O_3$	76.34	6.41	6.36
			1720	(440)	(76.39	6.39	6.29)
			1660 (C=N)				

a) Yield of isolated product. *b*) Colorless prisms (from isopropyl ether). *c*) Colorless needles (from benzene–isopropyl ether). *d*) Colorless prisms (from benzene–isopropyl ether).

TABLE II. ^{1}H-NMR Spectral Data for the Cycloadducts (**6**, **7**, and **8**) and the Cage Compounds (**12** and **13**)

Compd. No.	2-H	4-H	5-R	6-H	7-H	Me (s)	Me (s)	Ph (m)	CH_3–CH_2–O (q)	(t)
6a[a]	6.99 (dd)	7.89 (dd)	1.99 (d)	6.05 (m)	5.33 (m)	1.21	1.60	7.1—7.4	1.23	4.24
	$J_{2,4}=1.5$, $J_{2,7}=3.5$, $J_{4,6}=3$, $J_{4,5\text{-Me}}=1.5$, $J_{5\text{-Me},7}=1$, $J_{6,7}=6$ Hz									
6b[a]	6.99 (dd)	8.04 (dd)	3.37 (s)	5.26 (dd)	5.41 (dd)	1.25	1.59	7.1—7.4	1.25	4.25
	$J_{2,4}=1.5$, $J_{2,7}=3$, $J_{4,6}=3$, $J_{6,7}=7$ Hz									
7a[b]	7.67 (d)	3.88 (d)	1.78 (d)	5.43 (m)	4.98 (dd)	1.05	1.80	6.4—7.3	1.33	4.26
	$J_{2,7}=0.5$, $J_{4,6}=1.5$, $J_{5\text{-Me},6}=1$, $J_{6,7}=8$ Hz									
7b[b]	7.74 (d)	3.98 (d)	3.45 (s)	4.58 (dd)	5.17 (dd)	1.05	1.83	6.4—7.3	1.33	4.26
	$J_{2,7}=0.5$, $J_{4,6}=1.5$, $J_{6,7}=8$ Hz									
8a[b]	7.79 (d)	4.63 (d)	1.81 (d)	5.82 (m)	4.22 (dd)	0.94	1.85	6.4—7.7	1.31	4.28
	$J_{2,7}=0.5$, $J_{4,6}=1.5$, $J_{5\text{-Me},6}=1$, $J_{6,7}=7$ Hz									
8b[b]	7.67 (d)	4.27 (d)	3.35 (s)	4.64 (dd)	4.82 (dd)	0.88	1.81	6.3—7.6	1.27	4.17
	$J_{2,7}=0.5$, $J_{4,6}=1.5$, $J_{6,7}=7$ Hz									
12[b]	7.97 (d)	4.18 (s)	0.98 (s)	3.77 (d)	5.43 (dd)	1.23	1.43	6.6—7.2	1.20	1.40
	$J_{2,7}=0.5$, $J_{6,7}=6$ Hz									
13[b]	7.91 (d)	4.18 (s)	1.02 (s)	3.87 (d)	4.63 (dd)	1.05	1.32	6.8—7.2	1.30	4.28
	$J_{2,7}=0.5$, $J_{6,7}=6$ Hz									

a) δ in toluene-d_8 at 110 °C. *b*) δ in $CDCl_3$ at room temperature.

TABLE III. ^{13}C-NMR Chemical Shifts of Diazepine Ring Carbons of the Cycloadducts (**6a**, **7a**, and **8a**)[a,b]

Compd. No.	2-C	4-C	6-C	7-C
6a	78.9 (d)	158.8 (d)	135.3 (d)	61.2 (d)
7a	143.2 (d)	53.4 (d)	119.7 (d)	65.1 (d)
8a	142.2 (d)	55.5 (d)	127.5 (d)	61.2 (d)

a) δ in $CDCl_3$. *b*) The ^{13}C-NMR spectra of these adducts exhibited complex signals and thus were difficult to analyze precisely.

All products (**6**—**8**) gave elemental analyses and mass spectra (MS) consistent with formulations as the starting diazepines (**4**) plus one molecule of the cyclopentadienone (**5**), indicating the formation of 1 : 1 cycloadducts, and structural assignments of these products were mainly based on their infrared (IR) and nuclear magnetic resonance (NMR) spectral data, collected in Tables I, II, and III.

The IR spectra of the adducts (**6**) showed a highly strained carbonyl band at 1760 cm^{-1}; this strongly suggested the [6+4]π cycloadduct (**6**) or the [2+4]π cycloadduct (**9** or **10**) structure. The ^{1}H-NMR spectra of **6** showed a similar temperature dependence to those of 1,2-diazepines[10] and 2,3-benzodiazepines,[11] consistent with the predictable temperature-dependent inversion of the diazepine ring. Therefore, the spectra measured at room temperature exhibited complex split signals. However, the split signals coalesced completely at 110 °C to give the spectra summarized in Table II. In **6**, C-2 is bonded to two electronegative nitrogen atoms, while in **9** and **10**, only one sp^3 carbon is bonded to one nitrogen atom. The appearance of relatively low-field signals for 2-H (δ 6.99) and C-2 (δ 78.9) in the ^{1}H- and ^{13}C-NMR spectra of **6a** clearly indicates that the sp^3 carbon (C-2) in attached to two nirogen atoms. The chemical shift difference of 6-H between **6a** (δ 6.05) and **6b** (δ 5.26) is due to the difference of the substituents (Me for **6a**, OMe for **6b**) at the 5-position. These spectral data provide strong evidence for the proposed [6+4]π cycloadduct structure (**6**) and rule out the

other possible [2+4]π cycloadduct structures (**9** and **10**).

It is known that similar [2+4]π cycloadducts of the 1,3-oxazepine (**1**)[7] and azepines (**2**, **3**)[5,7] with cyclopentadienones readily undergo thermal [3,3]-sigmatropic rearrangement, a Cope rearrangement, giving rise to the corresponding [4+2]π cycloadducts similar to **7**, while a [6+4]π cycloadduct of **2** with a cyclopentadienone undergoes no rearrangement.[5] In the present case, even when the adducts (**6**) were heated in xylene at 140 °C for 10 d, no reaction occurred; this thermal behavior also supported the assignment of the [6+4]π cycloadduct structure to the products (**6**). In addition, irradiation (400 W, high-pressure Hg lamp) of **6** in benzene for 6 h afforded the bicyclic compounds (**11**) in *ca.* 85% yields. The formation of **11** from **6** may proceed by a photo-induced retro-reaction to the parent 1,3-diazepines (**4**), which are known[8] to undergo intramolecular cyclization to the bicyclic compounds (**11**) on irradiation.

On the other hand, both of the adducts (**7** and **8**) exhibited IR bands at 1720 (five-membered ring enone carbonyl) and 1690 (urethane carbonyl) cm^{-1} and showed no absorption due to strained carbonyl. The ^{1}H-NMR spectra of **7** and **8** broadly resembled each other, although the precise values of chemical shifts were different (Table II), suggesting that the adducts (**7** and **8**) are *regio*-isomers. The 4-H signal in the spectrum of **7a** appeared at higher field (δ 3.88) than that of **8a** (δ 4.63), while 7-H signal of **7a** appeared at lower field (δ 4.98) than that of **8a** (δ 4.22). These differences in chemical shifts may arise from the shielding effect of the phenyl group on the cyclopentenone ring, and thus the adducts (**7**) are considered to be *syn-endo* [4+2]π cycloadducts; consequently, the adducts (**8**) are *anti*-isomers. The structures of **7** and **8** were further confirmed by the following photochemical study.

Irradiation (220 W, high-pressure Hg lamp) of **7a** in benzene for 30 min resulted in an intramolecular [2+2]π cycloaddition to afford the cage compound (**12**) in 86% yield. Similarly, the adduct (**8a**), upon irradiation, gave the *regio*-isomeric cage compound (**13**) in 91% yield. The structures of **12** and **13** were elucidated from their spectral data given in Tables I and II. This photochemical behavior or **7** and **8** is analogous to that of the similar [4+2]π cycloadducts of the 1,3-oxazepine (**1**).

It has been reported[5-7] that the azepine derivatives (**1**—**3**) reacted with the cyclopentadienone (**5**) at 70—80 °C for 10—24 h to give the corresponding [2+4]π cycloadducts similar to **9** and the [4+2]π cycloadducts similar to **7**, and the former adducts were rearranged to the latter by further heating even at below 120 °C; however, the formation of [6+4]π cycloadducts was not observed. On the other hand, the 1*H*-azepine (**2**) is known to give a [4+6]π cycloadduct on treatment with 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone, along with the above two adducts.[5] On the basis of these results, possible reaction pathways for the present reaction are outlined in Chart 2. The formation of the [6+4]π cycloadducts (**6**) is assumed to occur from **4** and **5** directly, while those of the [4+2]π cycloadducts (**7** and **8**) may involve indirect pathways *via* the [2+4]π cycloadducts (**9** and **10**), respectively, although the direct pathways can not be ruled out. The reason why the key intermediates (**9** and **10**) have not been isolated in the present reaction of **4** with **5**, in contrast with the reactions of **1**—**3**, may be explained by the fact that the present addition required a higher temperature (140 °C) and a longer time (6 d for **4a**; 3 d for **4b**) than those for **1**—**3**, therefore, the adducts (**9** and **10**) presumably formed initially would have undergone Cope rearrangement under the drastic conditions to yield the [4+2]π cycloadducts (**7** and **8**, respectively). In conclusion, it should be noted that the present reaction affords the [6+4]π cycloadducts and two *regio*-isomers of [4+2]π cycloadducts, although the details of the mechanistic pathways and the reasons for the differences from the other azepine derivatives (**1**—**3**) are not clear.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Hitachi 270-30 spectrometer and MS were recorded on a JEOL DX-300 instrument. ^{1}H-NMR spectra were recorded on a JEOL JNM-MH100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise stated; spectral assignments were confirmed by spin-decoupling experiments. ^{13}C-NMR spectra were recorded on a JEOL FX-100 spectrometer. Microanalyses were performed in the Microanalytical Laboratory of this school by Mrs. R. Igarashi. Photolyses were carried out in an immersion apparatus equipped with a high-pressure Hg lamp and a Pyrex filter, which was cooled internally with running water.

Cycloaddition of Ethyl 5-Methyl-1*H*-1,3-diazepine-1-carboxylate (4a) with 2,5-Dimethyl-3,4-diphenylcyclopentadienone (5)——A solution of **4a** (616 mg) and **5** (1.07 g) in xylene (30 ml) was refluxed under N_2 for 6 d and then evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using *n*-hexane–ether as an eluent to give the adducts **8a** (467 mg, 31%), **6a** (109 mg, 7%), and **7a** (386 mg, 26%) successively. Physical, analytical, and spectral data are given in Tables I, II, and III.

Cycloaddition of Ethyl 5-Methoxy-1*H*-1,3-diazepine-1-carboxylate (4b) with 5——A solution of **4b** (706 mg) and **5** (1.0 g) in xylene (30 ml) was refluxed for 3 d and worked up as described for **4a** to give the adducts **6b** (495 mg, 30%), **8b** (203 mg, 12%), and **7b** (289 mg, 18%) successively. Physical, analytical, and spectral data are given in Tables I, II, and III.

Photolysis of the [6+4]π Cycloadducts (6a, b)——A solution of **6** (50 mg) in benzene (50 ml) was irradiated (400 W, high-pressure Hg lamp) for 6 h and then concentrated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2–*n*-hexane (1 : 1) as an eluent to give the ethyl 2,4-diazabicyclo[3.2.0]hept-3,6-dien-2-carboxylate **11a** (17 mg, 83%) and **11b** (20 mg, 86%), which were identical with authentic samples.

Photolysis of the *syn* [4+2]π Adduct (7a)——A solution of **7a** (50 mg) in benzene (50 ml) was irradiated (220 W, high-pressure Hg lamp) for 30 min and then evaporated to dryness *in vacuo*. The resulting solid residue was recrystallized from benzene–isopropyl ether to give the cage compound (**12**): 43 mg, 86% yield. Physical, analytical, and spectral data are given in Tables I and II.

Photolysis of the *anti* [4+2]π Adduct (8a)——A solution of **8a** (50 mg) in benzene (50 ml) was irradiated and worked up as described for **7a** to give the cage compound (**13**): 46 mg, 91% yield. Physical, analytical, and spectral data are given in Tables I and II.

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