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Studies on Diazepines. IX.[1] Difference between Photochemical and Thermal Rearrangements of 3H-1,2-Benzodiazepines into 3-Vinylindazoles

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The thermolysis of the 3-substituted 3H-1,2-benzodiazepines (**1**) afforded 1 : 1 mixtures of *trans*- (**2**) and *cis*- (**3**) 3-vinylindazoles, whereas their photolysis gave only the *trans*-isomers (**2**). The 3-substituted 5-methyl-3H-1,2-benzodiazepines (**4**) gave similar results. These findings suggest that the thermolysis occurs in a stepwise manner *via* the diradical intermediate (**9**), whereas the photolysis proceeds in a concerted manner.

Keywords——1,2-benzodiazepines; 3-vinylindazoles; photolysis; thermolysis; rearrangement; mechanism; ring contraction

We have already reported that the 3-unsubstituted 3H-1,2-benzodiazepines undergo both photochemical and thermal rearrangements to give the same 3-vinylindazoles in high yields.[3] Although these reactions were interpreted in terms of a diradical or concerted process, we were unable to elucidate the mechanisms. In connection with the similar rearrangements of other nitrogen-containing seven-membered ring systems, such as monocyclic 1,2-diazepines,[4] condensed 1,2-diazepines,[5] triazepines,[6] and benzoxazepines,[7] as well as the interesting thermal and photochemical stereospecific decompositions of five- and six-membered azocycloalkanes,[8] it seemed of general interest to examine the rearrangements of the 3H-1,2-benzodiazepines in more detail.

We report here that the photochemical and thermal rearrangements of the 3-substituted 3H-1,2-benzodiazepines (**1** and **4**) are different, and discuss the mechanistic features of these rearrangements with ring contraction.[9]

Thermolysis of 3-methoxy- (**1a**) and 3-acetoxy- (**1b**) 3H-1,2-benzodiazepine[3] in xylene at *ca.* 140° for 1.5—2 hr yielded a 1 : 1 mixture of the *trans*- (**2a, b**) and *cis*- (**3a, b**) 3-vinyl-1H-indazoles in the yields shown in Chart 1. However, irradiation of the diazepines (**1a, b**) with a high-pressure mercury lamp for 10—15 min using a Pyrex filter in methylene chloride solution gave the corresponding *trans*-3-vinyl-1H-indazoles (**2a, b**) in *ca.* 85% yields as the sole products. In both cases, the formation of products with loss of nitrogen, such as indenes, could not be observed.

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2) Location: *Kanagawa-machi, Kanazawa, 920-11, Japan.*
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7) C. Kaneko and R. Kitamura, *Heterocycles*, **6**, 111 (1977); and refs. cited therein.
8) For examples, W.P. Lay, K. Mackenzie, and J.R. Telford, *J. Chem. Soc.* (*C*), **1971**, 3199; E.L. Allred and A.L. Johnson, *J. Am. Chem. Soc.*, **93**, 1300 (1971); E.L. Allred and K.J. Voorhees, *ibid.*, **95**, 620 (1973); B.M. Trost, H.B. Neubold, P.H. Scudder, *ibid.*, **96**, 622 (1974); J.A. Berson, S.S. Olin, E.W. Petrillo, and P. Bickart, *Tetrahedron*, **30**, 1639 (1974); G. Greiner, M. Schneider, and H. Rau, *Tetrahedron Lett.*, **1976**, 4507.
9) Presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1977.

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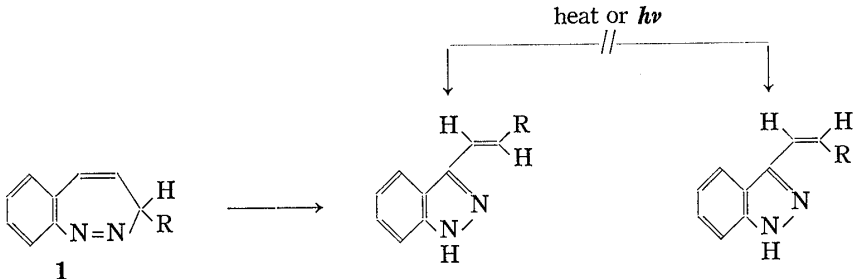
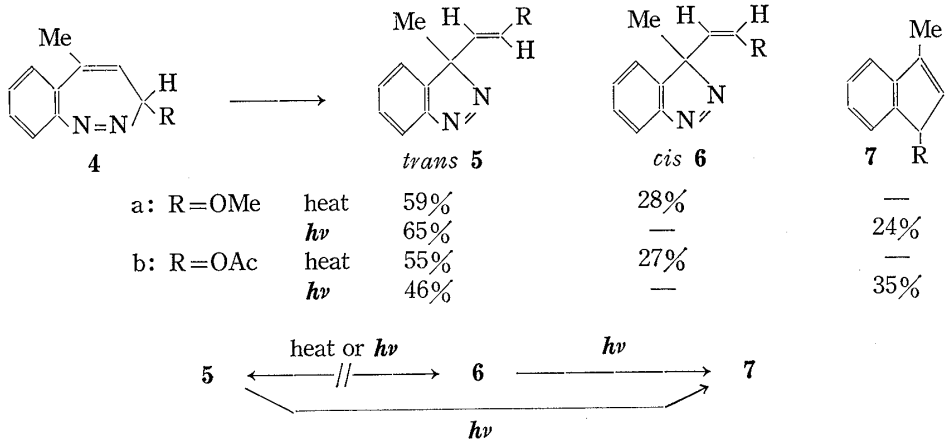


a: R=OMe	heat	43%	44%
	hv	86%	—
b: R=OAc	heat	45%	46%
	hv	84%	—

Chart 1

On the other hand, irradiation of the 5-methyl-3H-diazepines (**4a, b**)[3] resulted in the formation of the corresponding *trans*-3-vinyl-3H-indazoles (**5a, b**) and the indene derivatives (**7a, b**), whereas their thermolysis gave *trans*- (**5a, b**) and *cis*- (**6a, b**) 3-vinyl-3H-indazoles in the yields shown in Chart 2, and gave no indenes.



a: R=OMe	heat	59%	28%	—
	hv	65%	—	24%
b: R=OAc	heat	55%	27%	—
	hv	46%	—	35%

Chart 2

These products were characterized by microanalyses and by infrared (IR), nuclear magnetic resonance (NMR), and mass (MS) spectrometry. The assignments of *trans* and *cis* geometries to the olefin function in the 3-vinylindazoles (**2**, **3**, **5**, and **6**) were based on H–H coupling constants of 13 and 7 Hz, respectively. Either irradiation or thermolysis of the products (**2**) and (**3**) under the conditions used for their production resulted in recovery of almost all the starting indazoles unchanged. On the other hand, although heating of the 3H-indazoles (**5**) and (**6**) also resulted in recovery of the starting indazoles, they were converted to the corresponding indenes (**7**) by irradiation. These observations show that these products do not undergo *cis-trans* isomerization under the conditions employed for their formation and that the indenes are formed from the 3H-indazoles by loss of nitrogen and not directly from the 3H-diazepines.

The 3-unsubstituted 3H-1,2-benzodiazepines are known[3] to show a temperature-dependent inversion of the diazepine ring analogous to that observed for 4H-1,2-diazepines[10] and 2,3-benzodiazepines.[11] However, the ^{1}H NMR spectra of the 3-substituted diazepines (**1** and

10) O. Buchardt, C.L. Pedersen, U. Svanholm, A.M. Duffield, and A.T. Balaban, *Acta Chem. Scand.*, **23**, 3125 (1969).
11) A.A. Reid, J.T. Sharp, H.R. Sood, and P.B. Thorogood, *J. Chem. Soc. Perkin I*, **1973**, 2543.

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4) show no variation with temperature below 130°, and the molecules are apparently locked in the least-hindered conformation with the substituent group in the exo-position, as shown in the structure (**8**). New signals due to the products **2** and **3** or **5** and **6** appeared at 130° and increased in intensity with increasing temperature. However, no signals other than those of the products and the starting diazepines could be detected. This variable temperature spectral study demonstrates that the thermolysis involves neither ring inversion nor stable intermediates in the course of the above ring contraction of the 3-substituted diazepines (**1** and **4**).

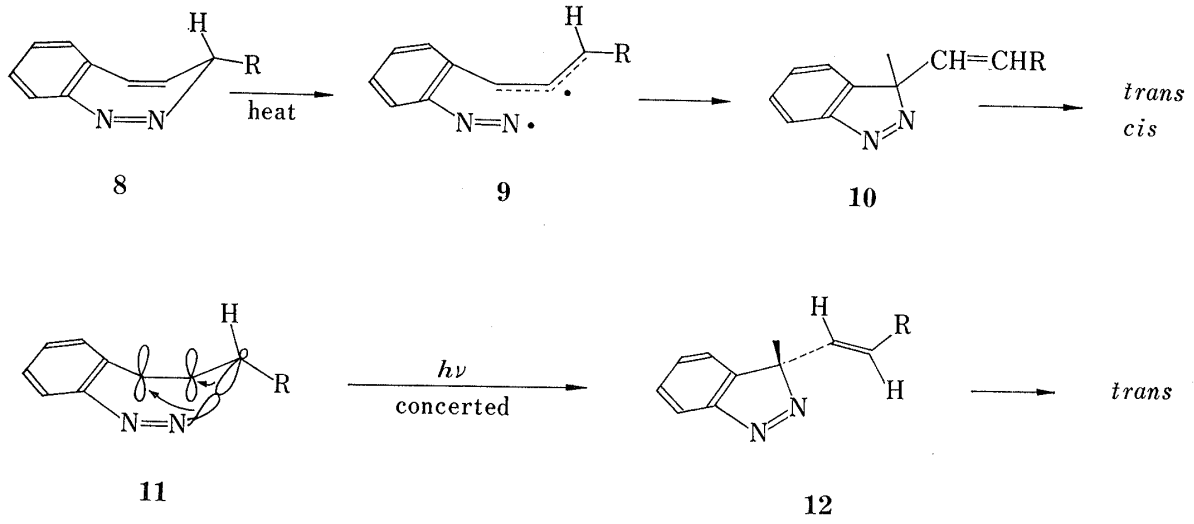

Chart 3

Based on these results, a plausible mechanism for the present ring contraction reactions is outlined in Chart 3. The thermal contraction may involve initial C–N bond fission to the diradical intermediates (**9**), with *trans-cis* isomerization followed by recombination to give the mixture of *trans*- and *cis*-3H-indazoles (**10**), although the radical intermediates could not be detected by CIDNP studies. It is known[12] that the rate of isomerization of allyl monoradicals is generally slower than the loss of nitrogen. However, it is likely that the *cis*⇆*trans* isomerization of the diradical (**9**) would be much faster than the radical recombination step, which might well occur before the loss of nitrogen. The stereospecific photochemical contraction may take a different mechanism, as depicted in Chart 3, which may involve a $_{\pi}2_{s}+_{\sigma}2_{s}$ concerted process to give only the *trans*-isomers (**12**), analogous to that proposed for 3,1-benzoxazepines,[7] although a radical process cannot be completely ruled out for this photolysis.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. IR spectra were determined with a JASCO IRA-2 spectrometer and MS spectra were obtained on a JEOL JMS-D100 instrument. NMR spectra were recorded on a JEOL JNM-MH100 spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard, and spectral assignments were confirmed by spin-decoupling experiments, and in the case of NH protons, by exchange with D_2O. Microanalyses were performed in the Microanalytical Laboratory of this school by Miss R. Hamano. Photolyses were carried out in an immersion apparatus equipped with a 200W high-pressure Hg lamp, which was cooled internally with running water.

Thermolysis of the 3H-diazepines (1a, b)——A solution of **1** (1 mmol) in xylene (3 ml) was refluxed for 2 hr and the reaction mixture was evaporated to dryness *in vacuo*. The resulting residue was chromatographed on silica gel to give **2** and **3** successively.

3-(*trans*-2′-Methoxyvinyl)-1H-indazole (**2a**): 43% yield, mp 82.5—84°, colorless prisms [from isopropyl ether (IPE)]. MS *m/e*: 174 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3150 (NH). NMR δ: 3.71 (3H, s, OMe), 6.12 (1H, d, $J=$

12) For a review, J.K. Kochi, "Free Radicals," Wiley Interscience, New York, 1973, Vol. II, p. 693.

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13 Hz), 7.48 (1H, d, J=13 Hz), 6.9—7.8 (4H, m, Ar–H), 10.0 (1H, br, NH). *Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.91; H, 5.77; N, 16.02.

3-(*cis*-2′-Methoxyvinyl)-1H-indazole (**3a**): 44% yield, mp 99—100°, colorless needles (from IPE). MS *m/e*: 174 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH). NMR δ: 3.77 (3H, s, OMe), 5.67 (1H, d, J=7 Hz), 6.26 (1H, d, J=7 Hz), 6.9—8.0 (4H, m, Ar–H), 10.5 (1H, br, NH). *Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.89; H, 5.81; N, 15.99.

3-(*trans*-2′-Acetoxyvinyl)-1H-indazole (**2a**): 45% yield, mp 116—118°, colorless needles (from benzene-IPE). MS *m/e*: 202 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1760 (C=O). NMR δ: 2.22 (3H, s, Ac-Me), 6.74 (1H, d, J=13 Hz), 7.0—7.9 (4H, m, Ar–H), 8.25 (1H, d, J=13 Hz), 10.8 (1H, br, NH). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.30; H, 5.00; N, 13.79.

3-(*cis*-2′-Acetoxyvinyl)-1H-indazole (**3b**): 46% yield, mp 104—106°, colorless needles (from IPE). MS *m/e*: 202 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1770 (C=O). NMR δ: 2.13 (3H, s, Ac–Me), 6.20 (1H, d, J=7 Hz), 7.0—8.1 (4H, m, Ar–H), 7.52 (1H, d, J=7 Hz), 9.5 (1H, br, NH). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.41; H, 4.92; N, 13.88.

Photolysis of 1a, b——A solution of **1** (1 mmol) in CH_2Cl_2 (150 ml) was irradiated with a high-pressure Hg lamp using a Pyrex filter for 10—15 min. After concentration *in vacuo*, the resulting residue was chromatographed on silica gel using CH_2Cl_2 as an eluent to give the 3-(*trans*-vinyl)-1H-indazoles (**2a**: 86%, **2b**: 84% yield).

Thermolysis of the 5-Methyl-3H-diazepines (4a, b)——A solution of **4** (1 mmol) in xylene (3 ml) was refluxed for 1.5—2 hr. After removal of the solvent *in vacuo*, the resulting residue was chromatographed on silica gel using *n*-hexane–ether mixture as an eluent to give **5** and **6** successively; these compounds were purified by rechromatography.

5-Methyl-3-(*trans*-2′-methoxyvinyl)-3H-indazole (**5a**): 59% yield, colorless oil. MS *m/e*: 188 (M^+). NMR δ: 1.58 (3H, s, 3-Me), 3.52 (3H, s, OMe), 5.12 (1H, d, J=13 Hz), 6.37 (1H, d, J=13 Hz), 7.4—8.2 (4H, m, Ar–H). *Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.01; H, 6.41; N, 14.79.

5-Methyl-3-(*cis*-2′-methoxyvinyl)-3H-indazole (**6a**): 28% yield, colorless oil. MS *m/e*: 188 (M^+). NMR δ: 1.64 (3H, s, 3-Me), 3.48 (3H, s, OMe), 4.65 (1H, d, J=7 Hz), 5.97 (1H, d, J=7 Hz), 7.3—8.2 (4H, m, Ar–H). *Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.87; H, 6.51; N, 14.75.

5-Methyl-3-(*trans*-2′-acetoxyvinyl)-3H-indazole (**5b**): 55% yield, colorless oil. MS *m/e*: 216 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (C=O). NMR δ: 1.60 (3H, s, 3-Me), 2.08 (3H, s, Ac–Me), 5.78 (1H, d, J=13 Hz), 7.23 (1H, d, J=13 Hz), 7.4—8.2 (4H, m, Ar–H). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.41; H, 5.66; N, 12.83.

5-Methyl-3-(*cis*-2′-acetoxyvinyl)-3H-indazole (**6b**): 27% yield, colorless oil. MS *m/e*: 216 (M^+). NMR δ: 1.64 (3H, s, 3-Me), 1.73 (3H, s, Ac–Me), 5.27 (1H, d, J=7 Hz), 7.06 (1H, d, J=7 Hz), 7.2—8.2 (4H, m, Ar–H). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.38; H, 5.68; N, 12.89.

Photolysis of 4a, b——A solution of **4** (1 mmol) in CH_2Cl_2 (150 ml) was irradiated with a high-pressure Hg lamp using a Pyrex filter for 5—6 min. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel using CH_2Cl_2 as an eluent to give the indenes (**7a**: 24%, **7b**: 35% yield) and 5-methyl-3-*trans*-vinyl)-3H-indazoles (**5a**: 65%, **5b**: 46% yield) successively.

1-Methoxy-3-methylindene (**7a**): colorless oil. MS *m/e*: 160 (M^+). NMR δ: 2.18 (3H, br s, 3-Me), 3.42 (1H, m, 1-H), 3.74 (3H, s, OMe), 5.72 (1H, m, 2-H), 7.2—7.9 (4H, m, Ar–H), $J_{2,3}$=3 Hz. *Anal.* Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.26; H, 7.61.

1-Acetoxy-3-methylindene (**7b**): colorless oil. MS *m/e*: 188 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O). NMR δ: 2.20 (3H, br s, 3-Me), 2.29 (3H, m, Ac–Me), 4.76 (1H, m, 1-H), 5.75 (1H, m, 2-H), 7.2—8.0 (1H, m, Ar–H), $J_{2,3}$=3 Hz. *Anal.* Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.52; H, 6.51.

Irradiation of 5a, b——A solution of **5** (50 mg) in CH_2Cl_2 (150 ml) was irradiated with a high-pressure Hg lamp using a Pyrex filter for 20 min. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel to give the corresponding indenes (**7**) in 80—85% yields.

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