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Studies on Diazepines. IV.[1] 3H-1,2-Benzodiazepines

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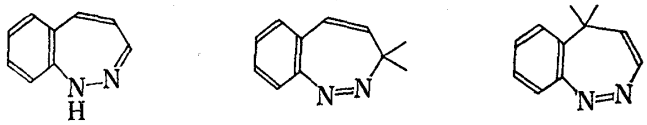
The previously unknown 3H-1,2- (**5**), 3-acetoxy-3H-1,2- (**6**), and 3-methoxy-3H-1,2- (**7**) benzodiazepines were prepared from the 1H-1,2-benzodiazepines (**1**) in high yields and the energy barriers to ring inversion for the 3H-diazepines (**5**) were estimated from nuclear magnetic resonance spectral data. Treatment of **5** with both bases and acids resulted in the tautomerization to give the 1H-isomers (**1**). However, the 3H-diazepines (**5**) gave 3-vinylindazoles (**8** or **9**) by thermolysis and gave the indazoles (**8** or **9**) and indenes (**10**) by photolysis in good yields, probably *via* the diradical (**11**) or the tetracyclic intermediates (**12**).

Keywords——diazepines; 3H-1,2-benzodiazepines; photolysis; thermolysis; isomerization; 3-vinylindazoles; indenes; temperature variable NMR; coalescence temperature; free energy of activation for ring inversion

The aza-cycloheptatrienes such as azepines, diazepines, and triazepines can in theory display annular tautomerism between one or more NH forms and various CH forms, and the tautomerism of these systems has been widely investigated.[3] As for the monocyclic 1,2-diazepines, all three different CH forms, *i.e.*, 3H-,[4] 4H-, and 5H-tautomers,[5] are known to be stable, however antiaromatic NH tautomers are unstable and can be isolated only as their iron tricarbonyl compounds[6] or N-substituted derivatives whose substituents are electron withdrawing groups such as acyl groups.[7] The 2,3-benzodiazepines are also known as two different CH tautomers and not as antiaromatic NH tautomers.[8]



1H-1 3H-2 5H-3

Chart 1

1) Part III: T. Tsuchiya, H. Arai, H. Hasegawa, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **25**, 2749 (1977).
2) Location: *Kanagawa-machi, Kanazawa, 920-11, Japan.*
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However, we have recently reported[9] the synthesis of the previously unknown, fully unsaturated 1H-1,2-benzodiazepines (**1**) which are the antiaromatic NH form, and we were interested in the preparation of the theoretically possible 3H-(**2**) and 5H- (**3**) tautomers in connection with the above-mentioned studies on tautomerism. We report here the syntheses of the 3H-1,2-benzodiazepines, one of CH forms, from 1H-diazepines (**1**) and some of their thermal and photochemical reactions, and their physical properties.[10]

The 2,3-dihydro-1H-1,2-benzodiazepines (**4**),[9] prepared by lithium aluminum hydride reduction of the 1H-1,2-benzodiazepines (**1**), were dehydrogenated with 4-phenyl-1,2,4-triazoline-3,5-dione in dry benzene to give the desired 3H-1,2-benzodiazepines (**5**) almost quantitatively.[11] Treatment of the 1H-diazepines (**1**) with lead tetraacetate in methylene

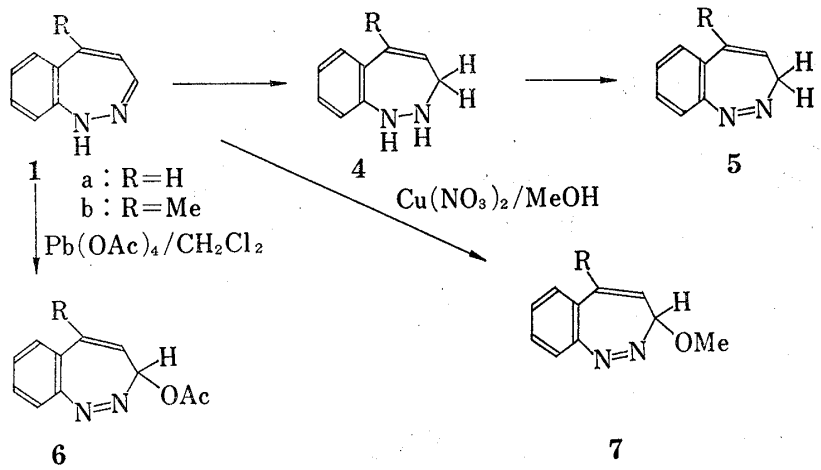

Chart 2

chloride and with anhydrous cuppric nitrate in absolute methanol also afforded the 3H-diazepines, 3-acetoxy-(**6**) and 3-methoxy- (**7**) -3H-1,2-benzodiazepines, respectively, in good yields.

The ^{1}H nuclear magnetic resonance (NMR) spectral data, on which will be described later in detail, are consistent with the proposed 3H-structures and eliminate the tautomeric 1H-, 2H-, and 5H-benzodiazepine structures. Complete characterization by infrared (IR), ultraviolet (UV), and mass (MS) spectrometry was also carried out for the new 3H-diazepines (**5**—**7**) (see Experimental Section).

The aza-cycloheptatrienes such as azepines,[4] diazepines,[12] and triazepines[13] have been known to be extremely susceptible to acid- and base-catalyzed, thermal, and photochemical rearrangements. Therefore, we examined such reactions of the diazepines (**5**).

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10) A part of this work has been published in a preliminary communication: T. Tsuchiya and J. Kurita, *J. Chem. Soc. Chem. Commun.*, **1974**, 936.
11) Direct tautomerization of **1** into **5** has not been successful to date.
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The 3H-diazepines (**5**) were readily tautomerized to the parent 1H-diazepines (**1**) by treatment with both bases and acids. Treatment of **5** with sodium methoxide in methanol gave **1** quantitatively and treatment with dry hydrogen chloride in ether also gave **1** in *ca.* 60% yield.

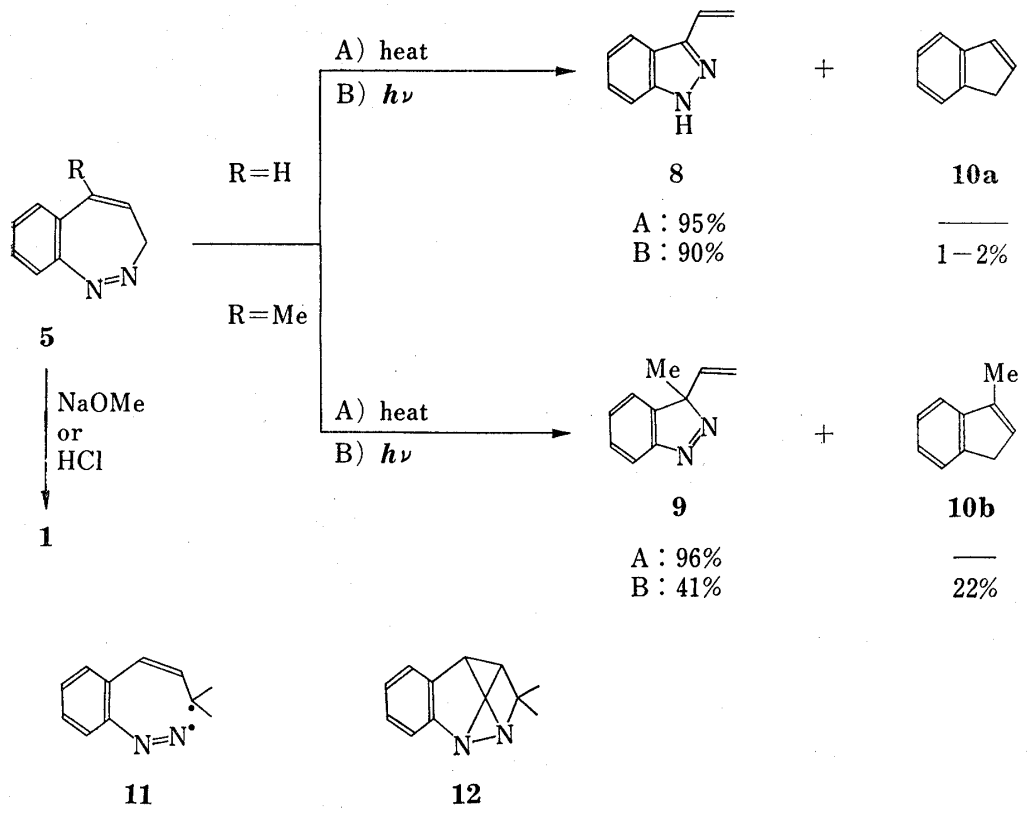

Chart 3

Next, **5a** was heated in xylene at 140° to give 3-vinyl-1H-indazole (**8**) in 95% yield. Under similar conditions, the 5-methyldiazepine (**5b**) gave the 3H-indazole (**9**) in 96% yield. On the other hand, irradiation of **5** in methylene chloride resulted in the formation of the 3-vinyl-indazole (**8** or **9**) and either indene (**10a**) or 3-methylidene (**10b**) in the yields shown in Chart 3. In the case of **5b**, a prolonged irradiation resulted in a decrease of the formation of **9** and an increase of **10b**.

These thermal and photochemical results indicate that the formation of **8** and **10** may involve proton transfer and extrusion of nitrogen of 3H-indazoles (**9**), which are formed *via* the diradical (**11**) or the tetracyclic (**12**) intermediates, and not tautomerization to the 1H- or 5H-isomers followed by $({}_{\pi}2_{s}+{}_{\pi}2_{s})$ cyclic addition of the aza-butadiene units to tricyclic compounds analogous to that observed for 2,3-benzodiazepines.[8b]

Finally, the ^{1}H NMR spectrum of the 3H-diazepines (**5**) showed a similar temperature dependence to those of 4H-1,2-diazepines[5a] and 1H- and 5H-2,3-benzodiazepines[8b] consistent with the predictable temperature-dependent inversion of the diazepine ring. As shown in Figure 1, the C-3 methylene protons (Ha and Hb) of **5a** show a doublet at δ 4.00 (**5b**: 3.98) at 100°, which broadens with decreasing temperature and splits into ABX quartets centered on δ 2.20 and 5.80 (**5b**: 2.22 and 5.67) below the coalescence temperature. The change is complete at −80° and the rest of the spectrum is essentially unchanged. The energies of activation for ring inversion were calculated by spectral analysis (see Table I).

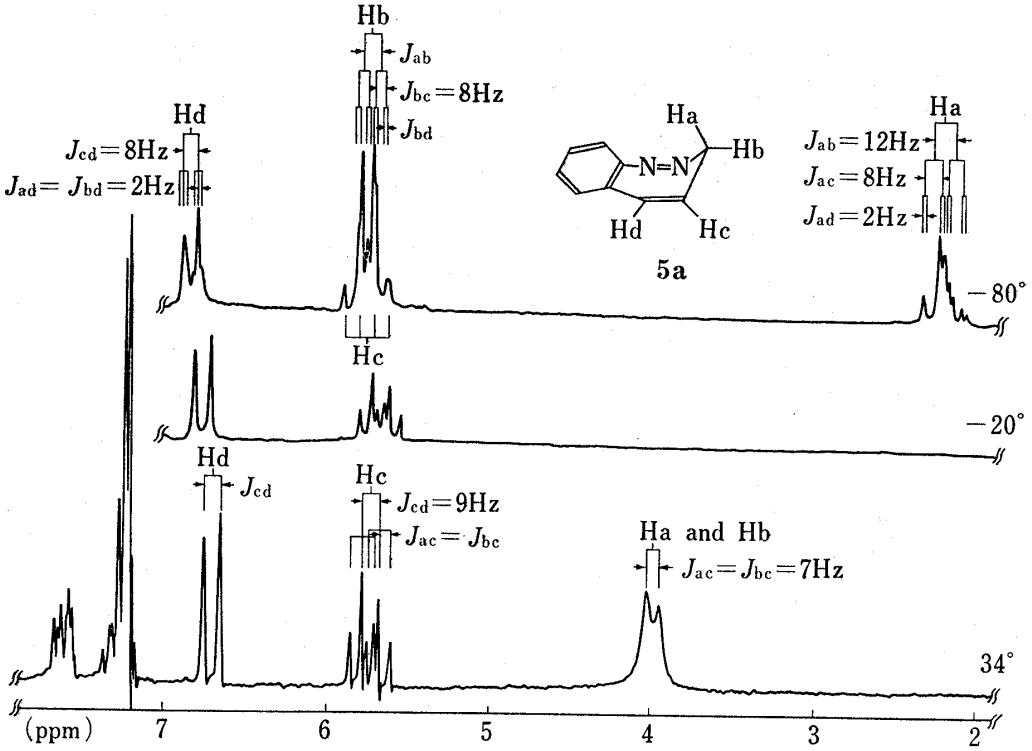

Fig. 1. NMR Spectra of 3H-1,2-Benzodiazepine (**5a**) at −80°, −20°, and 34° in CS_2

TABLE I. NMR Spectral Parameters for C-3 Methylene Groups in 3H-1,2-Benzodiazepines (**5**) at 90 MHz[a]

Compound	$\Delta\nu_{AB}$[b]/Hz (±1)	J_{AB}/Hz (±0.5)	T_c[c]/°C (±5)	$\Delta G^{\ddagger}$/kcal mol^{-1} at T_c[d]
5a	324.0	12	−20	11.7±0.3
5b	310.5	12	25	13.8±0.3

a) Spectra were measured on a Hitachi R-22 spectrometer in CS_2.
b) Chemical shift difference at −80° in Hz.
c) Temperature of coalescence.
d) The free energies of activation for ring inversion ($\Delta G^{\ddagger}$) were calculated using the formula: $k_c=\pi(\Delta\nu_{AB}^2+6J_{AB}^2)^{1/2}/\sqrt{2}$ [e]
e) G.J. Bishop, B.J. Price, and I.O. Sutherland, *Chem. Commun.*, **1976**, 672; and refs. cited therein.

The energy barriers to ring inversion are lower than those recorded for the monomeric 4H-diazepines[5a] (17—18 kcal mol^{-1}) and 2,3-benzodiazepines[8b] (19—20 kcal mol^{-1}). The $\Delta G^{\ddagger}$ value for **5b** increases most probably because of increased steric interaction in the transition state between 5-Me and the peri-hydrogen on the aromatic ring. However, the NMR spectra of the other diazepines (**6** and **7**) in which one of the C-3 hydrogens is substituted by a methoxy or an acetoxy group showed no variation with temperature. These molecules are apparently locked in the least hindered conformation with the substituent group in the exo-position.

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 JEOL JNM-MH100 and Hitachi R-22 spectrometers in $CDCl_3$ solution using tetramethylsilane as internal standard unless otherwise stated and spectral assignments were confirmed by spin-decoupling experiments and in the case of NH protons, by exchange with D_2O. UV

spectra were recorded on a Hitachi 323 spectrometer. 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 100W high-pressure Hg lamp, which was cooled internally with running water.

3H-1,2-Benzodiazepines (5a, b)——To a suspension of $LiAlH_4$ (0.5 g) in anhydrous ether (100 ml) cooled in an ice bath was added dropwise a solution of 1H-1,2-benzodiazepine (**1**, 1.0 g) in ether (50 ml) with stirring. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 15 min. The mixture was cooled in an ice bath and the excess reagent was decomposed with water. After removal of the resulting inorganic salts by filtration, the ether solution was dried over $MgSO_4$ and evaporated to dryness to give 2,3-dihydro-1H-1,2-benzodiazepine (**4**), which was dissolved in benzene (50 ml) without further purification. To the benzene solution was added a solution of 1-phenyl-1,2,4-triazoline-3,5-dione (1.1 g) in benzene (50 ml) with stirring. After stirring for an additional 10 min at room temperature, the resulting precipitate was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed over alumina using *n*-hexane–CH_2Cl_2 (3: 1) as eluent to give **5**.

5a: 952 mg (95% yield), yellow oil, bp_1 126—128° (bath temp.). MS *m/e*: 144 (M^+). UV λ_{max}^{EtOH} nm (ε): 225 (22000), 261 (9000). NMR (CS_2 at 20°) δ: 4.00 (2H, br d, 3-H), 5.75 (1H, m, 4-H), 6.72 (1H, d, 5-H), 7.2—7.8 (4H, m, Ar–H), $J_{3,4}$=7, $J_{4,5}$=9 Hz. *Anal.* Calcd. for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 74.71; H, 5.50; N, 19.22.

5b: 927 mg (93% yield), yellow oil, bp_1 132—134° (bath temp.). MS *m/e*: 158 (M^+). UV λ_{max}^{EtOH} nm (ε): 225 (25000), 261 (1000). NMR (CS_2, at 20°) δ: 2.12 (3H, br, 5-Me), 2.2—5.5 (2H, br, 3-H), 5.62 (1H, m, 4-H), 7.2—7.7 (4H, m, Ar–H). *Anal.* Calcd. for $C_{10}H_{10}N$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.73; H, 6.19; N, 17.51.

3-Acetoxy-3H-1,2-benzodiazepines (6a, b)——To a solution of **1** (500 mg) in CH_2Cl_2 (50 ml) cooled in an ice bath was added dropwise a solution of $Pb(OAc)_4$ (1.9 g) in CH_2Cl_2 (50 ml) with stirring. After stirring for an additional 30 min, the excess reagent was decomposed with water and the resulting precipitate was filtered off. The filtrate was successively washed with satd. $NaHCO_3$ and satd. NaCl, dried, and evaporated. The residue was chromatographed over silica gel using *n*-hexane–CH_2Cl_2 (2: 1) as eluent to give **6**.

6a: 620 mg (88% yield), mp 84—85°, yellow prisms [from isopropyl ether (IPE)]. MS *m/e*: 202 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). NMR δ: 2.27 (3H, s, Ac–Me), 4.62 (1H, dd, 3-H), 5.78 (1H, dd, 4-H), 6.72 (1H, dd, 5-H), 7.2—8.0 (4H, m, Ar–H), $J_{3,4}$=4, $J_{3,5}$=2, $J_{4,5}$=10 Hz. *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.23; H, 5.20; N, 13.81.

6b: 570 mg (83% yield), mp 62—63°, yellow prisms (from IPE). MS *m/e*: 216 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O). NMR δ: 2.12 (3H, m, 5-Me), 2.22 (3H, s, Ac–Me), 4.60 (1H, m, 3-H), 5.65 (1H, m, 4-H), 7.2—7.9 (4H, m, Ar–H). *Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.37; H, 5.43; N, 13.02.

3-Methoxy-3H-1,2-benzodiazepines (7a, b)——A mixture of **1** (2 mmol, a: 288 mg, b: 316 mg), anhydrous cuppric nitrate (2.2 mmol, 415 mg), and abs. MeOH was stirred for 24 hr at room temperature. The mixture was evaporated to dryness *in vacuo* below 40° and the residue was extracted with CH_2Cl_2. The extract was successively washed with satd. $NaHCO_3$ and satd. NaCl, dried, and evaporated. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give **7**.

7a: 269 mg (74% yield), mp 53—54°, yellow needles (from IPE). MS *m/e*: 174 (M^+), NMR δ: 3.28 (1H, dd, 3-H), 3.77 (3H, s, OMe), 5.76 (1H, dd, 4-H), 6.63 (1H, dd, 5-H), 7.1—7.9 (4H, m, Ar–H), $J_{3,4}$=4, $J_{4,5}$=10, $J_{3,5}$=2 Hz. *Anal.* Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.89; H, 5.75; N, 16.19.

7b: 167 mg (44% yield), yellow viscous oil. MS *m/e*: 188 (M^+). NMR δ: 2.18 (3H, m, 5-Me), 3.43 (1H, m, 3-H), 3.74 (3H, s, OMe), 5.75 (1H, m, 4-H). *Anal.* Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.85; H, 6.47; N, 14.62.

Treatment of 5a, b with MaOMe. Isomerization to 1——A mixture of the 3H-diazepine (**5**, 100 mg), NaOMe (20 mg), and MeOH (20 ml) was stirred for 4 hr at room temperature. The reaction mixture was evaporated to dryness below 30° and the residue was extracted with ether (100 ml). The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by chromatographed over alumina to give almost quantitatively the parent 1H-1,2-benzodiazepine (**1**), which was shown to be identical with authentic sample.

Thermolysis of 5a, b——A solution of **5** (100 mg) in xylene (3 ml) was refluxed for 2 hr and the reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel using *n*-hexane–CH_2Cl_2 mixture as eluent to give 3-vinyl-1H-indazole (**8**) from **5a** and 3-methyl-3-vinyl-3H-indazole (**9**) from **5b**.

8: 95 mg (95% yield), mp 117.5—118.5°, colorless prisms (from CH_2Cl_2–AcOEt). MS *m/e*: 144 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3150 (NH). NMR δ: 5.52 (1H, dd, J=11 and 1.5 Hz), 6.07 (1H, dd, J=16 and 1.5 Hz), 7.0 (1H, dd, J=11 and 16 Hz), 7.0—7.9 (4H, m, Ar–H), 11.0 (1H, br, NH). *Anal.* Calcd. for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.06; H, 5.51; N, 19.24.

9: 96 mg (96% yield), colorless oil. MS *m/e*: 158 (M^+). NMR δ: 1.50 (3H, s, 3-Me), 5.15 (1H, dd, J= 11 and 1.5 Hz), 5.20 (1H, dd, J=19 and 1.5 Hz), 6.70 (1H, dd, J=11 and 19 Hz), 7.3—8.2 (4H, m, Ar–H). *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.66; H, 6.36; N, 17.57.

Photolysis of 5a——A solution of **5a** (110 mg) in CH_2Cl_2 (150 ml) was irradiated with a high-pressure Hg lamp using a Pyrex filter for 30 min. After evaporation of the solvent *in vacuo*, the resulting residue was chromatographed over silica gel using CH_2Cl_2–AcOEt mixture as eluent to give indene (**10a**: 3 mg, 2% yield) and 3-vinyl-1H-indazole (**8**: 99 mg, 90% yield), successively.

Photolysis of 5b——A solution of **5b** (154 mg) in CH_2Cl_2 (150 ml) was irradiated for 18 min and worked up similarly to the procedure described for **5a** to give 3-methylindene (**10b**: 28 mg, 22% yield), the starting material (**5b**: 35 mg, 23% yield), and 3-vinyl-3H-indazole (**9**: 63 mg, 41% yield). However, irradiation for 40 min gave **9** (94 mg, 61%) as the sole product and not **10b**.