

Studies on Diazepines. V.¹⁾ Syntheses of 3-Substituted
1H-1,2-Benzodiazepines

TAKASHI TSUCHIYA and JYOJI KURITA

School of Pharmacy, Hokuriku University²⁾

(Received January 26, 1978)

Treatment of the 3H-1,2-benzodiazepine 2-oxides (8), prepared from the 3H-1,2-benzodiazepines (7) and *m*-chloroperbenzoic acid, with both acids and bases such as hydrogen chloride, acetic acid, sodium alkoxides, carbanions, and sodium cyanide afforded the corresponding previously unknown 3-substituted 1,2-benzodiazepines (10–17) in moderate yields.

Keywords—diazepines; 1,2-benzodiazepines; 3H-1,2-benzodiazepine N-oxides; 3-substituted 1H-1,2-benzodiazepines; reactions of N-oxides; base-catalyzed reaction; acid-catalyzed reaction

In previous papers we have reported³⁾ the general synthesis of the fully unsaturated 1H-1,2-benzodiazepine and their derivatives having various substituents in all except the 3-position by photo-induced ring expansion of the corresponding N-iminoquinolinium ylide dimers (2) *via* the N-ylides (1). However, 3-substituted 1,2-benzodiazepines have not been prepared by the method because 2-substituted quinolines do not yield N-ylide dimers, and little is known about them. To our knowledge, only two examples have been reported; *viz.* (i) cyclopenta-1,2-benzodiazepines (4)⁴⁾ from 2-diphenylmethylenecyclopentanone tosylhydrazones, and (ii) 3-ethoxycarbonyl-1,2-benzodiazepines (5)⁵⁾ from chloroglyoxylate phenylhydrazones bearing

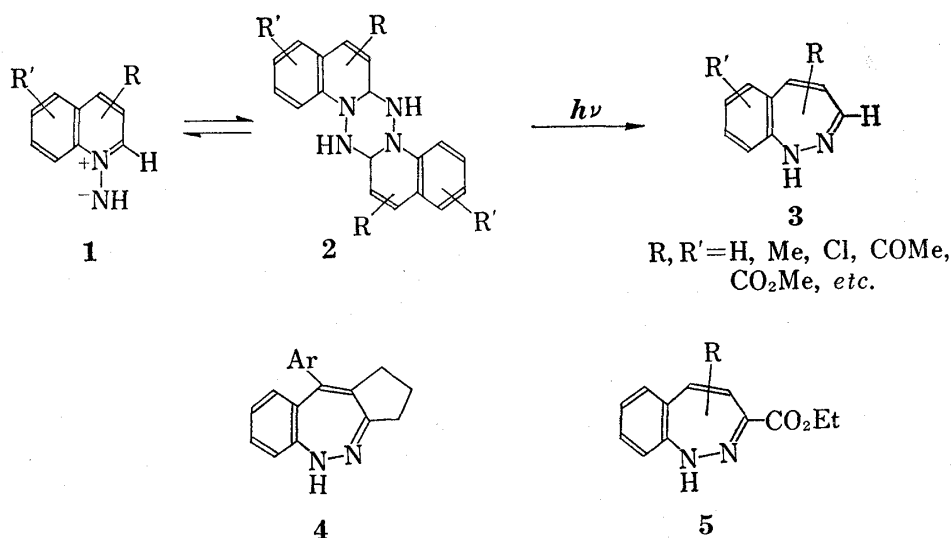


Chart 1

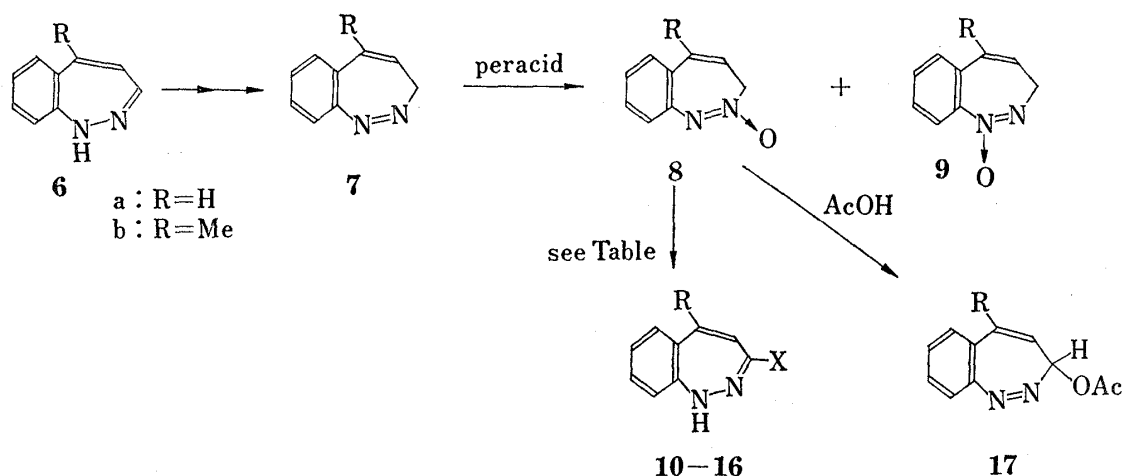
- 1) Part IV: T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull.* (Tokyo), **26**, 1890 (1978).
- 2) Location: Kanagawa-machi, Kanazawa, 920-11, Japan.
- 3) T. Tsuchiya, J. Kurita, H. Igeta, and V. Snieckus, *J. Chem. Soc. Chem. Commun.*, **1974**, 440; T. Tsuchiya, J. Kurita, and V. Snieckus, *J. Org. Chem.*, **42**, 1856 (1977).
- 4) J. T. Sharp, R. H. Findlay, and P. B. Thorogood, *J. Chem. Soc., Perkin I*, **1975**, 102; J. Dingwall and J. T. Sharp, *J. Chem. Soc. Chem. Commun.*, **1975**, 128; and refs. cited therein.
- 5) L. Garanti, A. Scandroglio, and G. Zecchi, *Tetrahedron Lett.*, **1975**, 3349; L. Garanti and G. Zecchi, *J. Chem. Soc. Perkin I*, **1977**, 2092.

an α,β -unsaturated substituent in the *ortho*-position by treatment with triethylamine. However, both methods are inapplicable to other 3-substituted diazepines as general synthetic procedures.

We now report a general route to previously unknown 3-substituted 1,2-benzodiazepines from 1H-1,2-benzodiazepines *via* 3H-1,2-benzodiazepine N-oxides.⁶⁾

The 3H-1,2-benzodiazepines (7), prepared by lithium aluminum hydride reduction of the 1H-1,2-benzodiazepines (6) followed by dehydrogenation,¹⁾ were oxidized with 1.1 molar equivalent of *m*-chloroperbenzoic acid in methylene chloride and chromatographed over alumina to give the 2-oxides (8) and the 1-oxides (9) in yields of 60–65% and 20–22%, respectively. When an excess of the peracid was used, the N-oxides were further oxidized to yield their 4,5-epoxides.

The position of the N-oxide group in 8 and 9 was established by the ¹H-nuclear magnetic resonance (NMR) spectral data (see Experimental Section). The signal of the C-9 proton of the 1-oxides (9) was found at lower field (about δ 8.0) than were the other signals of the protons in the benzene ring. However, this is not the case with the spectra of the 2-oxides (8). It is apparent that the low-field shift of the C-9 proton signals of the 1-oxides should be ascribed to the anisotropic effect of the N–O group by analogy with cases of benzazine and benzodiazine N-oxides such as quinoline, cinnoline, and quinazoline 1-oxides.⁷⁾



No.	X	Reagent/Solvent
10	Cl	dry HCl/ether
11	OMe	NaOMe/MeOH
12	OEt	NaOEt/EtOH
13	CH(CO ₂ Me) ₂	CH ₂ (CO ₂ Me) ₂ -NaOMe/MeOH
14	CN	KCN/MeOH
15	CO ₂ Me	
16	CONH ₂	

Chart 2

The desired 3-substituted benzodiazepines were obtained in moderate yields by treatment of the 2-oxides (8) with both bases and acids. Treatment of 8 with dry hydrogen chloride in ether resulted in the formation of the 3-chlorodiazepines (10) in *ca.* 90% yield. The reaction of 8 with sodium methoxide in methanol and with sodium ethoxide in ethanol gave the 3-methoxy- (11) and 3-ethoxy-diazepines (12) in yields of 60–70% and *ca.* 10%, respectively. In these cases, the parent quinolines were also obtained.

6) A part of this work has been published in a preliminary communication: T. Tsuchiya and J. Kurita, *J. Chem. Soc. Chem. Commun.*, 1976, 419.

7) K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull. (Tokyo)*, 11, 681 (1963).

As an example of the reaction with carbanions, the reaction of **8** with dimethyl malonate in the presence of an equivalent of sodium methoxide in methanol gave the 3-[bis(methoxycarbonyl)methyl]diazepines (**13**) in 60% yield and the parent quinolines in 15–20% yield.

Although the reaction of **8** with hydrogen cyanide in ether did not give the expected cyano derivatives in contrast to the case of hydrogen chloride, treatment with sodium cyanide in methanol containing small amount of water resulted in the formation of the 3-cyanodiazepines (**14**), 3-methoxycarbonyldiazepines (**15**), and 3-carbamoyldiazepines (**16**) in yields of *ca.* 15%, 30%, and 35%, respectively. This result indicates that the reaction may involve the initial formation of the 3-cyanodiazepines (**14**) in *ca.* 80% yield, followed by hydrolysis to give **16** and by methanolysis to give **15** in the reaction condition.

Finally, treatment with acetic acid led to the 3-acetoxy-3H-diazepines (**17**) in *ca.* 50% yield. However, attempts to obtain 3-alkyl and 3-phenyldiazepines by treatment of **8** with Grignard reagents have not been successful to date. All the new benzodiazepines obtained were characterized by elemental analysis and infrared, nuclear magnetic resonance, and mass spectroscopy and spectral comparison with the 1,2-benzodiazepines already reported.^{3–5)}

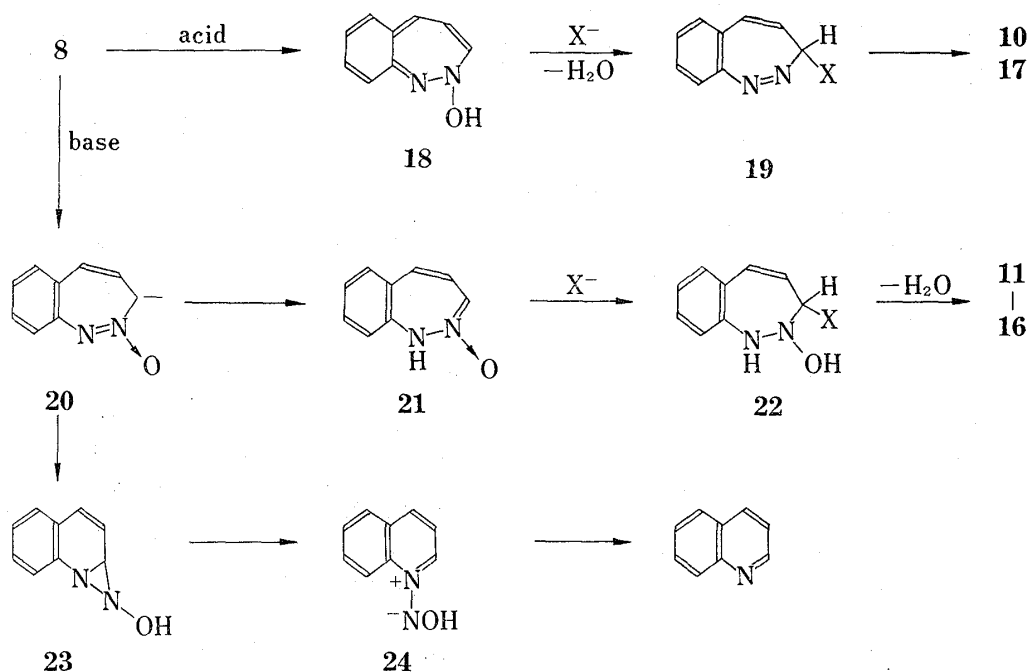


Chart 3

A possible mechanism for these reactions is shown in Chart 3. The acid-catalyzed reaction may involve initial protonation at the N-oxide oxygen and subsequent elimination of a 3-hydrogen to the intermediate (**18**), followed by addition of the nucleophile to give the 3H-isomer (**19**). 3H-1,2-Benzodiazepines are known readily to undergo tautomerization to their 1H-isomers.¹⁾ However, the acetoxy compounds (**17**), which were also obtained by treatment of **8** with lead tetraacetate,¹⁾ do not tautomerize. The base-catalyzed reaction may proceed by two competing paths: (i) isomerization to the 1H-diazepines (**21**) *via* **20**, followed by addition of the nucleophiles to give the diazepines (**11–16**); (ii) cyclization to the diaziridine intermediates (**23**), followed by ring-opening to give the parent quinolines *via* the ylides (**24**).

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were determined with a JASCO IRA-2 spectrometer and mass (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 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 . Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer. Microanalyses were performed in the Micro-analytical laboratory of this school by Miss. R. Hamano.

N-Oxidation of 3H-1,2-Benzodiazepine (7a)—To a solution of **7a** (2.6 g) in CH_2Cl_2 (100 ml) cooled in an ice bath was added dropwise a solution of *m*-chloroperbenzoic acid (4.3 g) in CH_2Cl_2 (80 ml) with stirring. After stirring for an additional 1 hr at room temperature, the excess reagent was decomposed with 100 ml of 10% Na_2SO_3 . The organic layer was washed with water, dried over MgSO_4 , and evaporated to dryness. The resulting residue was chromatographed over alumina to give the 2-oxides (**8a**) from the eluate with isopropyl ether (IPE)-*n*-hexane (1:1) and the 1-oxides (**9a**) from the eluate with IPE.

8a: 1.60 g (55% yield), mp 85–86° (colorless prisms, from benzene-IPE). MS m/e : 160 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 222 (16000), 310 (1300). NMR δ : 4.56 (2H, d, 3-H), 6.14 (1H, m, 4-H), 7.07 (1H, d, 5-H), 7.2–7.6 (4H, m, Ar-H), $J_{3,4}=7$, $J_{4,5}=9$ Hz. Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.71; H, 4.79; N, 17.73.

9a: 0.65 g (22% yield), mp 93–94° (colorless prisms, from benzene-IPE). MS m/e : 160 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 223 (23000), 310 (1700). NMR δ : 3.95 (2H, br d, 3-H), 6.65 (1H, m, 4-H), 6.84 (1H, d, 5-H), 7.2–7.6 (3H, m, Ar-H), 8.03 (1H, m, 9-H), $J_{3,4}=7$, $J_{4,5}=9$ Hz. Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.46; H, 4.75; N, 17.28.

N-Oxidation of 5-Methyl-3H-1,2-benzodiazepine (7b)—To a solution of **7b** (2.24 g) in CH_2Cl_2 (100 ml) was added a solution of *m*-chloroperbenzoic acid (3.4 g) in CH_2Cl_2 (60 ml) and worked up similarly to the procedure described for **7a** to give the 2-oxide (**8b**) and the 1-oxide (**9b**).

8b: 1.55 g (63% yield), mp 68–69° (colorless prisms, from benzene-IPE). MS m/e : 174 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 235 (29000), 303 (5800). NMR δ : 2.25 (3H, m, 5-Me), 4.34 (2H, br, d, 3-H), 5.97 (1H, m, 4-H), 7.0–7.6 (4H, m, Ar-H), $J_{3,4}=7$, $J_{3,5-\text{Me}}=J_{4,5-\text{Me}}=1$ Hz. Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.97; H, 5.61; N, 15.84.

9b: 0.49 g (20% yield), mp 93–94° (colorless prisms, from benzene-IPE). MS m/e : 174 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 234 (31000), 306 (5600). NMR δ : 2.16 (3H, m, 5-Me), 3.4 and 4.2 (2H, br, d, 3-H), 6.10 (1H, m, 4-H), 7.3–7.6 (3H, m, Ar-H), 7.92 (1H, m, 9-H), $J_{3,4}=7$, $J_{3,5-\text{Me}}=J_{4,5-\text{Me}}=1$ Hz. Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.15; H, 5.70; N, 15.78.

3-Chloro-1H-1,2-benzodiazepines (10a, b)—A mixture of the 2-oxide (**8**, 170 mg) and saturated dry ethereal hydrogen chloride (6 ml) in an ice bath was stirred for *ca.* 5 hr and then evaporated *in vacuo*. The residue was basified with 2% NaHCO_3 and extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , and evaporated to dryness. The resulting residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give **10**.

10a: 163 mg (86% yield), mp 68–69° (yellow prisms, from IPE). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3260 (NH). NMR δ : 6.01 (1H, d, $J=11$ Hz, 4-H), 6.6 (1H, br, NH), 6.82 (1H, d, 5-H). Anal. Calcd. for $\text{C}_9\text{H}_7\text{ClN}_2$: C, 60.51; H, 3.95; N, 15.68. Found: C, 60.50; H, 3.83; N, 15.38.

10b: 174 mg (89% yield), mp 86–87° (yellow prisms, from IPE). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3280 (NH). NMR δ : 2.21 (3H, d, $J=1$ Hz, 5-Me), 6.10 (1H, m, 4-H), 6.6 (1H, br, NH). Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{ClN}_2$: C, 62.34; H, 4.71; N, 14.54. Found: C, 62.65; H, 4.70; N, 14.25.

3-Methoxy-1H-1,2-benzodiazepines (11a, b)—To a solution of the 2-oxide (**8**, 200 mg) in methanol (5 ml) was added excess sodium methoxide (150 mg) and the mixture was stirred for 18 hr at room temperature. The reaction mixture was evaporated to dryness *in vacuo* and the residue was extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , and evaporated to dryness. The residue was chromatographed over silica gel using *n*-hexane-IPE (1:1) to give **11**.

11a: 143 mg (66% yield), mp 85–86° (yellow prisms, from IPE). MS m/e : 174 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3260 (NH). NMR δ : 3.65 (3H, s, OMe), 6.04 (1H, d, $J=11$ Hz, 4-H), 6.88 (1H, d, 5-H). Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.84; H, 5.57; N, 15.83.

11b: 115 mg (55% yield), mp 94–95° (yellow prisms, from IPE). MS m/e : 188 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3290 (NH). NMR δ : 2.17 (3H, d, $J=1$ Hz, 5-Me), 3.58 (3H, s, OMe), 5.96 (1H, m, 5-H). Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.20; H, 6.39; N, 14.69.

Besides **11**, quinoline (17% yield, from **8a**) and lepidine (35% yield, from **8b**) were also obtained from the eluate with IPE, respectively.

3-Ethoxy-1H-1,2-benzodiazepines (12a, b)—A mixture of **8** (200 mg), ethanol (10 ml), and sodium ethoxide (200 mg) was worked up similarly to the procedure described for **11** to give **12** and the parent quinolines (quinoline: 70% yield from **8a**; lepidine: 72% yield from **8b**).

12a: 24 mg (10% yield), mp 63.5–65° (yellow prisms, from IPE). MS m/e : 188 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3270 (NH). NMR δ : 1.22 (3H, t, Me), 4.04 (2H, q, CH_2), 6.10 (1H, d, 4-H), 6.92 (1H, d, 5-H). Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.20; H, 6.39; N, 15.00.

12b: 22 mg (9% yield), mp 91–93° (yellow prisms, from IPE). MS m/e : 202 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3290 (NH). NMR δ : 1.25 (3H, t, Me), 2.22 (3H, d, 5-Me), 4.04 (2H, q, CH_2), 6.13 (1H, m, 4-H). Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.30; H, 6.99; N, 13.89.

3-[Bis(methoxycarbonyl)methyl]-1H-1,2-benzodiazepines (13a, b)—To a solution of dimethyl malonate (1 g) and sodium methoxide (0.5 g) in abs. methanol (10 ml) was added dropwise a solution of **8** (200 mg) in methanol (3 ml) with stirring. The reaction mixture was stirred for an additional 3 hr at room temperature and then was neutralized with AcOH. After removing the solvent *in vacuo*, the residue was extracted with CH_2Cl_2 . The extract was washed successively with satd. NaHCO_3 and water, dried over MgSO_4 , and then evaporated. The resulting residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give **13**.

13a: 168 mg (59% yield), viscous oil. MS m/e : 274 (M^+). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3350 (NH), 1750 (C=O). NMR δ : 3.73 (6H, s, OMe), 4.41 (1H, s, $-\text{CH}$), 6.11 (1H, d, $J=11$ Hz, 4-H), 6.84 (1H, d, 5-H). Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.39; H, 5.21; N, 9.98.

13b: 157 mg (47% yield), viscous oil. MS m/e : 288 (M^+). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3350 (NH), 1750 (C=O). NMR δ : 2.21 (3H, d, $J=1$ Hz, 5-Me), 3.73 (6H, s, OMe), 4.39 (1H, s, $-\text{CH}$), 6.18 (1H, m, 4-H). Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.51; H, 5.67; N, 9.66.

Treatment of the 2-Oxide (8a) with Sodium Cyanide—A mixture of **8a** (1.0 g), NaCN (2.0 g), and abs. MeOH (40 ml) was stirred for 20 hr at room temperature. The reaction mixture was evaporated to dryness *in vacuo* below 20° and the residue was extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , and evaporated. The residue was chromatographed over silica gel to give 3-cyano-1H-1,2-benzodiazepine (**14a**) and 3-methoxycarbonyl-1H-1,2-benzodiazepine (**15a**) from the eluate with IPE, and 3-carbamoyl-1H-1,2-benzodiazepine (**16a**) from the eluate with IPE-AcOEt (1:1), successively.

14a: 142 mg (13% yield), mp $70-71^\circ$ (dark red plates, from IPE). MS m/e : 169 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300 (NH), 2200 (CN). NMR δ : 5.58 (1H, d, $J=11$ Hz, 4-H), 6.47 (1H, d, 5-H), 6.8 (1H, br, NH). Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{N}_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.87; H, 4.13; N, 24.74.

15a: 412 mg (33% yield), mp $128-130^\circ$ (dark red plates, from IPE-benzene). MS m/e : 202 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250 (NH), 1705 (C=O). NMR δ : 3.82 (3H, s, OMe), 6.30 (1H, d, $J=11$ Hz, 4-H), 6.61 (1H, d, 5-H), 7.9 (1H, br, NH). Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.34; H, 4.97; N, 13.85.

16a: 386 mg (33% yield), mp $189-191^\circ$ (dark red plates, from IPE-benzene). MS m/e : 187 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450 and 3250 (NH), 1670 (C=O). NMR (d_5 -pyridine) δ : 6.58 (1H, d, $J=12$ Hz, 4-H), 6.85 (1H, d, 5-H), 6.8 (3H, br, NH). Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.24; H, 4.85; N, 22.24.

Treatment of the 2-Oxide (8b) with Sodium Cyanide—A mixture of **8b** (500 mg), NaCN (1 g), and abs. MeOH (30 ml) was worked up similarly to the procedure described for **8a** to give 3-cyano-5-methyl- (**14b**), 3-methoxycarbonyl-5-methyl- (**15b**), and 3-carbamoyl-5-methyl- (**16b**) 1H-1,2-benzodiazepine.

14b: 65 mg (12% yield), mp $67-68^\circ$ (red needles, from IPE). MS m/e : 183 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250 (NH), 2200 (CN). NMR δ : 2.16 (3H, d, $J=1$ Hz, 5-Me), 5.83 (1H, m, 4-H), 7.1 (1H, br, NH). Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.00; H, 4.92; N, 23.03.

15b: 162 mg (26% yield), mp $159-160^\circ$ (orange prisms, from IPE-benzene). MS m/e : 216 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250 (NH), 1710 (C=O). NMR δ : 2.21 (3H, d, $J=1$ Hz, 5-Me), 3.81 (3H, s, OMe), 6.44 (1H, m, 4-H), 6.9 (1H, br, NH). Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.67; H, 5.59; N, 13.01.

16b: 197 mg (34% yield), mp $228.5-230^\circ$ (yellow needles, from EtOH). MS m/e : 201 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 and 3200 (NH), 1650 (C=O). NMR (d_5 -pyridine) δ : 2.05 (3H, d, $J=1$ Hz, 5-Me), 6.99 (1H, m, 4-H), 7.1 (3H, br, NH). Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.51; H, 5.48; N, 20.83.

3-Acetoxy-3H-1,2-benzodiazepines (17a, b)—A solution of **8** (100 mg) in AcOH (2 ml) was refluxed for 5 hr and then the reaction solution was evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel using CH_2Cl_2 -*n*-hexane mixture as eluent to give **17**, which were shown to be identical to authentic samples¹ by mixture melting point and NMR spectral comparison.

17a: 56 mg (44% yield), mp $84-85^\circ$.

17b: 63 mg (51% yield), mp $62-63^\circ$.