[Chem. Pharm. Bull. 28(6)1842—1846(1980)]

# Studies on Diazepines. XI.[1] Oxidation of 1H-1,2-Benzodiazepines with Lead Tetraacetate: Formation and Some Reactions of Novel 5H-1,2-Benzodiazepines

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(Received January 8, 1980)

Treatment of 1H-1,2-benzodiazepines having an electron-withdrawing group such as methoxycarbonyl or cyano in the 3-position with lead tetraacetate resulted in the formation of the corresponding 5-acetoxy-5H-1,2-benzodiazepines, which are the first reported examples of 5H-1,2-benzodiazepines. The 5H-diazepines, on treatment with base, underwent tautomerization to the 1H-isomers, and on photolysis gave 3-acetoxyindole *via* the tricyclic valence isomers. Furthermore, treatment of a 5H-diazepine with methanol or acetic acid gave the corresponding 4-methoxy- or 4-acetoxy-4,5-dihydro-1H-1,2-benzodiazepine, respectively, by 1,4-addition of the reagent.

**Keywords**——1H-1,2-benzodiazepines; 3H-1,2-benzodiazepines; 5H-1,2-benzodiazepines; 3-vinylindazoles; 3-acetoxyindole; lead tetraacetate oxidation; photolysis; tautomerism

The tautomerism of aza-cycloheptatrienes such as azepines, diazepines, and triazepines has been widely investigated.[3] As for the monomeric 1,2-diazepines, all three different CH forms, *i. e.*, 3H-,[4] 4H-, and 5H-tautomers,[5] are known to be relatively stable, but the antiaromatic NH tautomers, 8$\pi$-electron aza-analogs of the cycloheptatrienyl anion, are unstable and can be isolated only as their iron tricarbonyl complexes[6] or N-substituted derivatives[7] with electron-withdrawing substituents such as acyl groups. The 2,3-benzodiazepines also have two CH tautomers and no antiaromatic NH forms.[8] However, we have reported the synthesis of the fully unsaturated 1H-1,2-benzodiazepines (**1**)[9] and their analogs,[10] which are antiaromatic NH forms, and reported the conversion[11] of **1** into 3H-tautomers (**2**), one of the two theoretically possible CH forms. The 1H-1,2-diazepines (**1**) are more stable than the 3H-tautomers (**2**) which are readily tautomerized to the 1H-isomers (**1**) by both bases and acids, and are also susceptible to thermal and photochemical rearrangements,[11,12] but direct tautomerization of the 1H- and 3H-tautomers into 5H-tautomers (**3**), another possible CH form, has not been achieved.

1) Part X: T. Tsuchiya, K. Takayama, and J. Kurita, *Chem. Pharm. Bull.*, **27**, 2476 (1979).
2) Location: *Kanagawa-machi, Kanazawa 920-11, Japan.*
3) For a review, see J. Elguero, C. Martin, A.R. Katritzky, and P. Linda, "Advances in Heterocyclic Chemistry Supplement 1, The Tautomerism of Heterocycles," Academic Press, New York, 1976.
4) C.D. Anderson, J.T. Sharp, H.R. Sood, and R.S. Strathdee, *J. Chem. Soc. Chem. Commun.*, **1975**, 613; C.D. Anderson, J.T. Sharp, and R.S. Strathdee, *J. Chem. Soc. Perkin I*, **1979**, 2209.
5) O. Buchardt, C.L. Pedersen, U. Svanholm, A.M. Duffield, and A.T. Balaban, *Acta Chem. Scand.*, **23**, 3125 (1969); A.T. Balaban, *Tetrahedron*, **26**, 739 (1970).
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9) T. Tsuchiya, J. Kurita, and V. Snieckus, *J. Org. Chem.*, **42**, 1856 (1977).
10) T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Heterocycles*, **9**, 621 (1978); T. Tsuchiya, M. Enkaku, J. Kurita, and H. Sawanishi, *Chem. Pharm. Bull.*, **27**, 2183 (1979).
11) J. Kurita and T. Tsuchiya, *J. Chem. Soc. Chem. Commu.*, **1974**, 936; T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull.*, **26**, 1890 (1978).
12) T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull.*, **27**, 2523 (1979).

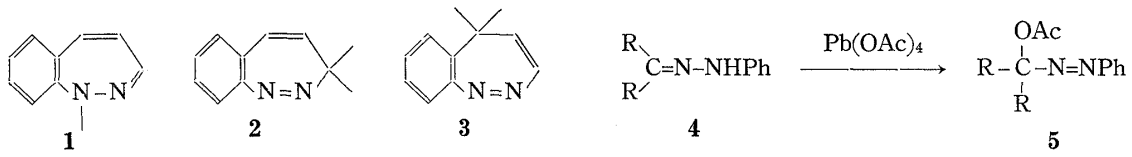

Chart 1

Therefore, we were interested in the preparation of the 5H-1,2-benzodiazepines, and now describe the synthesis of the first reported examples of 5H-diazepines and some of their reactions.[13]

It has been shown that lead tetraacetate reacts with ketone phenylhydrazones (**4**) to form azoacetates (**5**) in good yields.[14] Therefore, 1H-1,2-benzodiazepines having the phenylhydrazone moiety in the ring were expected to give similar results, and we have previously reported[11] that the treatment of unsubstituted 1H-1,2-benzodiazepine (**6a**) with lead tetraacetate gave 3-acetoxy-3H-1,2-benzodiazepine (**7a**). Furthermore, formation of 5-acetoxy-5H-1,2-benzodiazepines was also considered to be possible because of the presence of the conjugated diene system. Thus, we further examined the oxidative behavior of various 3-substituted diazepines.

Treatment of the 3-methoxydiazepine (**6b**)[15] with lead tetraacetate in methylene chloride gave methyl cinnamate (**8b**) in 75% yield *via* the 3H-diazepine (**7b**), whose formation was confirmed by nuclear magnetic resonance (NMR) spectral analysis of the residue obtained by concentration of the reaction solution. However, **7b** was unstable and decomposed to give **8b** during isolation. Similar oxidation of the 3-methoxycarbonyldiazepine (**6c**)[15] resulted in the formation of the desired 5-acetoxy-5H-diazepine (**9c**) and the 3-vinylindazole (**10c**) in 68% and 25% yields, respectively.

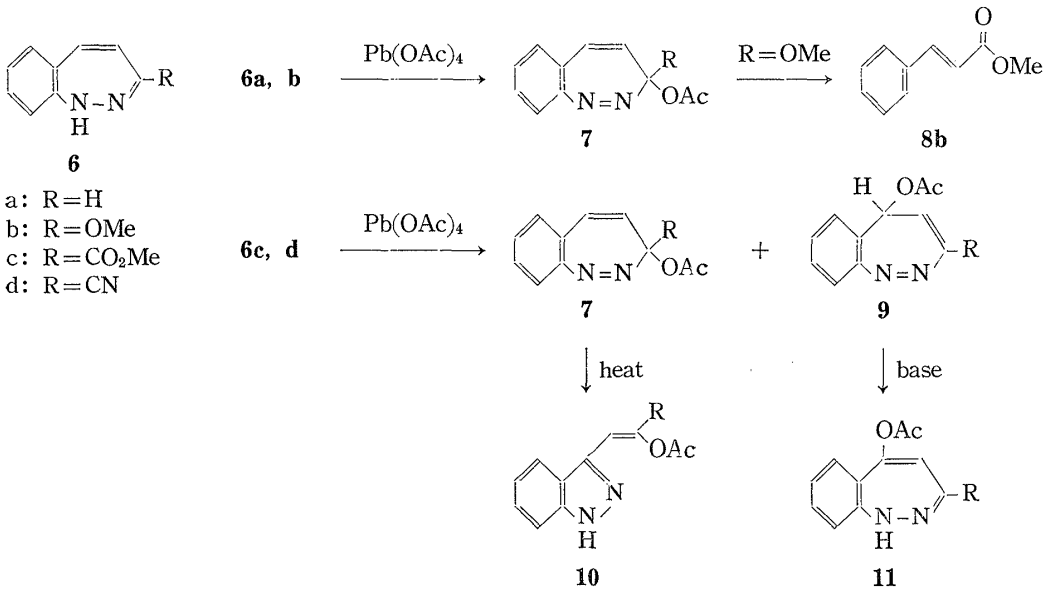

Chart 2

The 3H-1,2-benzodiazepines are known to be extremely susceptible to heat- and light-induced rearrangements to give 3-vinylindazoles in high yields.[11] Thus, the indazole (**10c**)

13) A part of this work has been published in a preliminary communication: T. Tsuchiya and J. Kurita, *J. Chem. Soc. Chem. Commun.*, **1979**, 803.
14) D.C. Iffland, L. Salisbury, and W.R. Schafer, *J. Am. Chem. Soc.*, **83**, 747 (1961).
15) T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull.*, **26**, 1896 (1978).

might be formed *via* the 3H-diazepine (**7c**). The 5H-diazepine (**9c**) thus obtained was readily tautomerized into the 1H-isomer (**11c**) by treatment with triethylamine in benzene. Similarly, oxidation of the 3-cyanodiazepine (**6d**)[15] with lead tetraacetate yielded the 5H-diazepine (**9d**) and the 3-vinylindazole (**10d**) in *ca.* 70% and 24% yields, respectively. However, the 5H-diazepine (**9d**) was unstable and gradually decomposed during isolation. Thus, the reaction mixture was treated with triethylamine without separation to give the stable 5-acetoxy-1H-diazepine (**11d**). It should be noted that an electron-withdrawing group is required for the formation of 5H-diazepines in the present oxidation.

The diazepines (**9**) are first reported examples of 5H-1,2-benzodiazepine derivatives, and their $^{1}H$- and $^{13}C$-NMR spectral data are consistent with the proposed structures. As stated in the introductory paragraphs, the aza-cycloheptatrienes are known to be susceptible to acid- and base-catalyzed, thermal, and photochemical rearrangements. Therefore, we examined such reactions of the new 5H-diazepine (**9c**).

The 3H-1,2-benzodiazepines are readily tautomerized into their 1H-isomers by treatment with both weak and strong bases. However, while the 5H-diazepines (**9**) were also tautomerized into the 1H-isomers (**11**) by a weak base such as triethylamine or pyridine in benzene, treatment of **9** with a strong base such as sodium hydroxide or sodium alkoxide resulted in decomposition to give no characterizable products. The 1H-diazepine (**11c**) was further treated with triethylamine in methanol instead of benzene to give the 5-oxodiazepine (**12**) in *ca.* 80% yield.

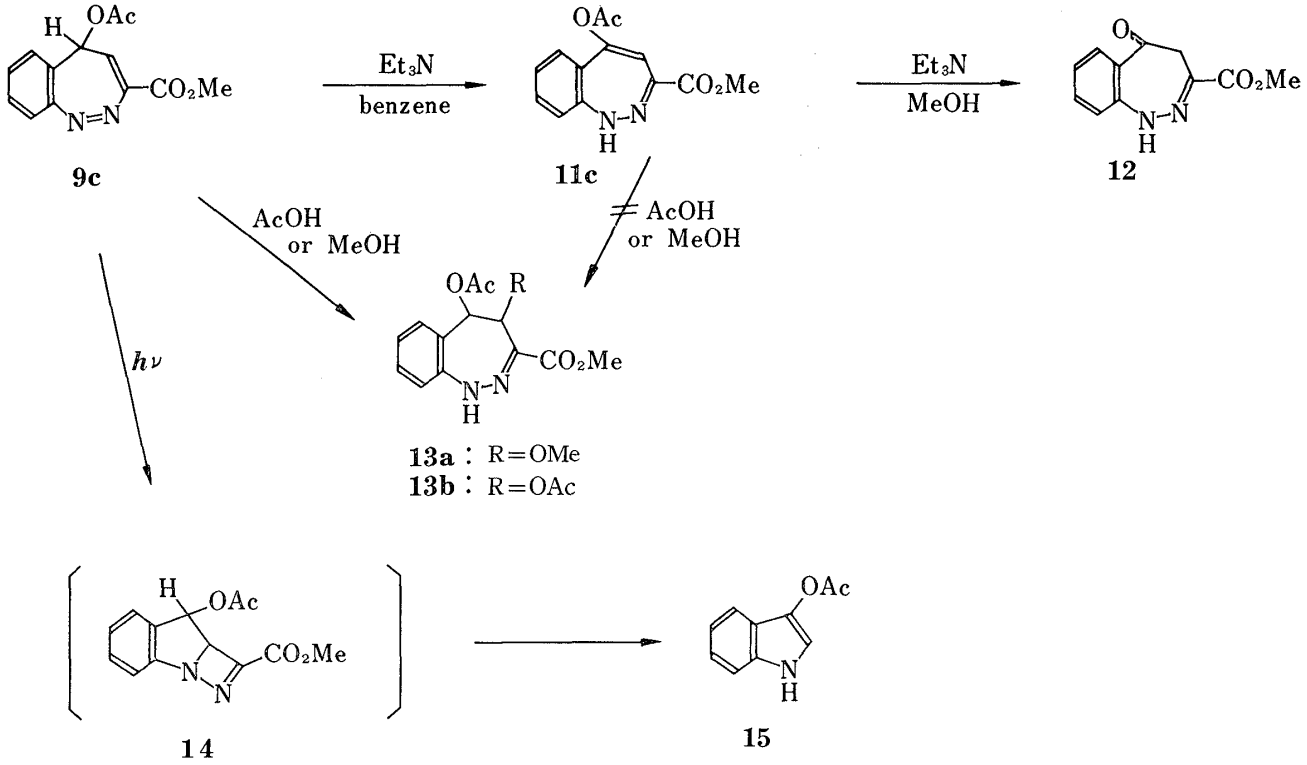


Chart 3

Next, a solution of the 5H-diazepine (**9c**) in methanol or in benzene containing acetic acid was stirred for 2—3 days at room temperature to give the corresponding adduct (**13**) in 70—75% yield. The adducts (**13**) were not obtained from the 1H-diazepine (**11c**) by similar treatments, so they are presumably formed directly from **9c** by 1,4-addition of the reagents. When the 5H-diazepine (**9c**) was heated in xylene at 100—140°, it decomposed, giving no

characterizable products, in contrast to the 3H-tautomers, which give indazoles by a rearrangement with ring contraction.

Finally, irradiation of **9c** with a halogen lamp in methylene chloride for *ca.* 10 min gave 3-acetoxyindole (**15**) in 75% yield; this may be formed *via* the tricyclic valence isomer (**14**) followed by extrusion of ethyl cyanoformate, by analogy with the behavior observed for 3H-1,2-diazepines,[16] 2,3-benzodiazepines,[8] and triazepines.[17] This photochemical behavior of **9** is also different from that of 1H- and 3H-1,2-benzodiazepines.

In conclusion, these results and those already reported clearly indicate that in the three 1,2-benzodiazepine tautomers the antiaromatic NH form is the most stable and the stability is in the order 1H->3H->5H-tautomer.

## 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 recorded on a JEOL JMS-D100 instrument. NMR spectra were recorded on JEOL JNM-MH100 and FX-100 spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise stated, and spectral assignments were confirmed by spin-decoupling experiments and, in the case of NH protons, by exchange with $D_2O$. 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 halogen lamp (Ushio, JCV-200W-GS), which was cooled internally with running water.

**Oxidation of 3-Methoxy-1H-1,2-benzodiazepine (6b) with Lead Tetraacetate**——A solution of $Pb(OAc)_4$ (640 mg) in $CH_2Cl_2$ (10 ml) was added dropwise with stirring to a solution of the 1H-diazepine (**6b**, 174 mg) in $CH_2Cl_2$ (20 ml), cooled in an ice bath. After stirring for an additional 10 min at room temperature, 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, then dried over $MgSO_4$, and concentrated *in vacuo* below 30°. The resulting residue contained 3-acetoxy-3-methoxy-3H-1,2-benzodiazepine (**7b**, *ca.* 80%), the identity of which was confirmed by the $^1$H-NMR spectrum of the residue [$\delta$: 1.64 (3H, s, OAc), 3.61 (3H, s, OMe), 6.07 (1H, d, 4-H), 6.77 (1H, d, 5-H), 7.2—8.1 (4H, m, Ar–H), $J_{4,5}$=11 Hz]. However, the product (**7b**) decomposed readily to give methyl cinnamate[18] (**8b**, 121 mg, 75%) during purification by chromatography on silica gel or alumina using $CH_2Cl_2$ as an eluent.

**Oxidation of 3-Methoxycarbonyl-1H-1,2-benzodiazepine (6c) with Lead Tetraacetate**——A solution of $Pb(OAc)_4$ (900 mg) in $CH_2Cl_2$ (15 ml) was added dropwise with stirring to a solution of the 1H-diazepine (**6c**, 303 mg) in $CH_2Cl_2$ (30 ml), cooled in an ice bath. After stirring for an additional 15 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, then dried, and concentrated *in vacuo*. The residue (338 mg) was chromatographed on Sephadex (LH-20), eluting with $CHCl_3$ to give **9c**. Further elution with $CHCl_3$–EtOH (10: 1) gave **10c**.

5-Acetoxy-3-methoxycarbonyl-5H-1,2-benzodiazepine (**9c**): 265 mg, 68% yield, orange oil. MS *m/e*: 260 ($M^+$). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1735 (C=O). $^1$H-NMR $\delta$: 2.08 (3H, s, OAc), 3.85 (3H, s, OMe), 5.66 (1H, d, 5-H), 6.78 (1H, d, 4-H), 7.2—8.0 (4H, m, Ar–H), $J_{4,5}$=6 Hz. $^{13}$C-NMR $\delta$: 20.4 (q), 52.9 (q), 66.8 (d, 5-C), 124.1 (d), 128.9 (d), 129.4 (d), 131.3 (d and s), 131.7 (d), 139.1 (s), 148.5 (s), 163.4 (s), 169.5 (s). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.25; H, 4.58; N, 10.57.

3-(2′-Acetoxy-2′-methoxyvinyl)-1H-indazole (**10c**): 97 mg, 25% yield, mp 148—150°, colorless needles (from AcOEt). MS *m/e*: 260 ($M^+$). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3250 (NH), 1770 (C=O), 1700 (C=O). NMR ($d_6$-acetone) $\delta$: 2.24 (3H, s, OAc), 3.78 (3H, s, OMe), 7.57 (1H, s, 1′-H), 7.0—8.0 (4H, m, Ar–H). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.82; H, 4.61; N, 10.61.

**Oxidation of 3-Cyano-1H-1,2-benzodiazepine (6d) with Lead Tetraacetate**——A solution of $Pb(OAc)_4$ (900 mg) in $CH_2Cl_2$ (15 ml) was added dropwise with stirring to a solution of the 1H-diazepine (**6d**, 254 mg) in $CH_2Cl_2$ (30 ml), cooled in an ice bath. After stirring for an additional 10 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, then dried, and concentrated *in vacuo*. The $^1$H-NMR spectrum of the resulting residue showed that the residue was a mixture of 5-acetoxy-3-cyano-5H-1,2-benzodiazepine (**9d**) [$\delta$: 2.03 (3H, s, OAc), 5.64 (1H, d, 5-H), 6.47 (1H, d, 4-H), $J_{4,5}$=6 Hz] and **10d** in a ratio of *ca.* 3: 1; however, the former product (**9d**) was unstable and gradually decomposed during separation. Therefore, the residue

16) C.D. Anderson, J.T. Sharp, E. Stefaniuk, and R.S. Strathdee, *Tetrahedron Lett.*, **1976**, 305.
17) D.J. Anderson and A. Hassner, *J. Chem. Soc. Chem. Commun.*, **1974**, 45; V. Nair, *J. Heterocycl. Chem.*, **12**, 183 (1975); T. Tsuchiya, J. Kurita, and K. Ogawa, *J. Chem. Soc. Chem. Commun.*, **1976**, 250.
18) These authentic samples were obtained from Tokyo Kasei Kogyo Co., Ltd, Tokyo, Japan.

was dissolved in dry benzene (20 ml) without separation and triethylamine (0.5 ml) was added to the solution. After stirring for 15 hr at room temperature, the reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using $CH_2Cl_2$–AcOEt (10: 1) as an eluent to give **11d** and **10d** successively.

5-Acetoxy-3-cyano-1H-1,2-benzodiazepine (**11d**): 203 mg, 60% yield, mp 128—130°, red needles [from benzene–isopropyl ether (IPE)]. MS *m/e*: 227 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300 (NH), 2300 (CN), 1770 (C=O). NMR $\delta$: 2.22 (3H, s, OAc), 5.69 (1H, s, 4-H), 6.4—7.3 (4H, m, Ar-H), 6.9 (1H, br, NH). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.27; H, 4.01; N, 18.55.

3-(2′-Acetoxy-2′-cyanovinyl)-1H-indazole (**10d**): 82 mg, 24% yield, mp 78—80°, colorless prisms (from benzene–IPE). MS *m/e*: 227 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3200 (NH), 2300 (CN), 1760 (C=O). NMR $\delta$: 2.38 (3H, s, OAc), 6.9 (1H, br, NH), 7.19 (1H, s, 1′-H), 7.1—7.8 (4H, m, Ar–H). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.66; H, 4.06; N, 18.17.

**Treatment of 9c with Triethylamine in Benzene**——A mixture of the 5H-diazepine (**9c**, 50 mg), triethylamine (300 mg), and benzene (10 ml) was allowed to stand in the dark for 15 hr at room temperature. After concentration *in vacuo*, the resulting residue was chromatographed on silica gel, using $CH_2Cl_2$ as an eluent, to give 5-acetoxy-3-methoxycarbonyl-1H-1,2-benzodiazepine (**11c**): 44 mg, 88% yield, mp 120—122°, red prisms (from benzene-IPE). MS *m/e*: 260 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300 (NH), 1770 (C=O), 1740 (C=O). NMR $\delta$: 2.22 (3H, s, OAc), 3.75 (3H, s, OMe), 6.22 (1H, s, 4-H), 6.4—7.1 (4H, m, Ar–H), 7.2 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.87; H, 4.61; N, 10.82.

**Treatment of 11c with Triethylamine in Methanol**——A mixture of the 1H-diazepine (**11c**, 36 mg), triethylamine (100 mg), and methanol (1 ml) was allowed to stand for 5 hr at room temperature. The resulting crystals were collected and recrystallized from MeOH to give 3-methoxycarbonyl-5-oxo-1,4-dihydro-1,2-benzodiazepine (**12**): 21 mg, 70% yield, mp 184—186°, colorless needles. MS *m/e*: 218 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300 (NH), 1710 (C=O), 1660 (C=O). NMR $\delta$: 3.83 (2H, s, 4-H), 3.94 (3H, s, OMe), 7.0—8.2 (4H, m, Ar–H), 9.2 (1H, br, NH). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.34; H, 4.58; N, 12.68.

**Treatment of 9c with Methanol**——A solution of **9c** (51 mg) in MeOH (2 ml) was allowed to stand for 3 days at room temperature in the dark and then evaporated to dryness *in vacuo*. The resulting solid was recrystallized from AcOEt to give 5-acetoxy-4-methoxy-3-methoxycarbonyl-4,5-dihydro-1H-1,2-benzodiazepine (**13a**): 41 mg, 72% yield, mp 165—167°, colorless prisms. MS *m/e*: 292 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3250 (NH), 1750 (C=O), 1720 (C=O). NMR $\delta$: 1.92 (3H, s, OAc), 3.32 (3H, s, OMe), 3.94 (3H, s, OMe), 5.27 (1H, d, 4-H), 6.28 (1H, d, 5-H), 7.0—7.6 (4H, m, Ar–H), 9.4 (1H, br, NH), $J_{4,5}$=7 Hz. *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.22; H, 5.67; N, 9.46.

**Treatment of 9c with Acetic Acid**——A mixture of **9c** (47 mg), AcOH (50 mg), and benzene (2 ml) was stirred for 16 hr at room temperature in the dark and then $CH_2Cl_2$ (50 ml) was added to the reaction solution. The mixture was successively washed with satd. $NaHCO_3$ and satd. NaCl, then dried, and evaporated to dryness *in vacuo*. The resulting crystalline solid was recrystallized from AcOEt to give 4,5-diacetoxy-3-methoxycarbonyl-4,5-dihydro-1H-1,2-benzodiazepine (**13b**): 43 mg, 74% yield, mp 173—175°, colorless prisms. MS *m/e*: 320 ($M^+$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3250 (NH), 1750 (C=O), 1720 (C=O). NMR $\delta$: 1.79 (3H, s, OAc), 1.95 (3H, s, OAc), 3.96 (3H, s, OMe), 6.37 (1H, d, 4- or 5-H), 6.54 (1H, d, 4- or 5-H), 7.0—7.6 (4H, m, Ar–H), 10.0 (1H, br, NH), $J_{4,5}$=7 Hz. *Anal.* Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.05; N, 8.75. Found: C, 55.99, H, 5.04; N, 8.78.

**Photolysis of 9c**——A solution of **9c** (93 mg) in $CH_2Cl_2$ (150 ml) was irradiated with a halogen lamp using a Pyrex filter for 7—8 min. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel, using $CH_2Cl_2$–AcOEt (5: 1) as an eluent, to give 3-acetoxyindole (**15**: 46 mg, 74% yield, mp 131—132°), which was identical with an authentic sample.[18]

**Acknowledgement** A part of this work was supported by a Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.