[Chem. Pharm. Bull. 25(10)2749—2754(1977)]

UDC 547.892.04 : 541.14.04 : 546.21-1.04

Photo-oxygenation of 1H-1,2-Diazepine and Azepine Derivatives: Formation and Some Reactions of Their Epidioxides

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(Received May 18, 1977)

The photo-sensitized oxygenation of 1,2-diazepines (**1** and **12**) and azepine (**17**) results in the formation of the corresponding relatively stable epidioxides (**2**, **13**, and **18**). The dioxides (**2**) react with potassium hydroxide to give the epoxy-ketones (**10**) and with methanol to give the solvent adducts (**11**), probably *via* the intermediates (**8** and **9**). Treatment of **13** with alumina gives the hydroxy-epoxide (**15**), which is converted to the epoxy-diazepinone (**16**) by an alkali treatment. However, a similar treatment of **18** with bases gives only N-ethoxycarbonylaniline (**19**) and does not give any other characterized products.

Keywords——photo-sensitized oxygenation; singlet oxygen; (4+2) π cycloaddition; 1H-1,2-diazepines; azepines; epidioxides of 1,2-diazepines; epidioxide of azepine; isomerization of epidioxides

The dye-sensitized photooxygenation has been the object of extensive study over the years and various N-heterocycles[2] and seven-membered conjugated trienes, such as cycloheptatrienes[3] and tropolones,[4] have also been investigated. However, oxygenation of aza-cycloheptatrienes is little known, except for a recent paper on 2-phenyl-1,3-oxazepine.[5]

On the other hand, 1H-1,2-diazepines were first prepared photochemically from N-iminopyridinium ylides by Streith ,*et al.*[6] and the chemistry of the diazepines has been widely studied.[7,8]

Therefore, it seemed of interest to examine the photooxidative behaviour of 1H-1,2-diazepines and azepines in connection with the above mentioned studies. We report the formation of the corresponding 4,7-epidioxides from the diazepines (**1** and **12**) and azepine (**17**) by dye-sensitized oxygenation and the results of some reactions of the dioxides thus obtained.[9]

The diazepines (**1a—e**) were prepared from the corresponding N-acylaminopyridinium ylides by photo-induced ring expansion reaction.[7] A solution of **1** in methylene chloride

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2) For examples: L.K. Low and D.A. Lightner, *Chem. Commun.*, **1972**, 625; *Idem*, *J. Heterocycl. Chem.*, **12**, 789 (1975); H.H. Wasserman, J.R. Scheffer, and J.L. Cooper, *J. Am. Chem. Soc.*, **94**, 4991 (1972).
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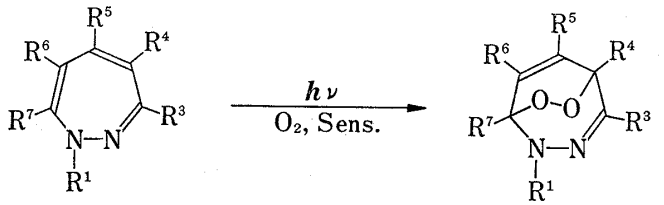
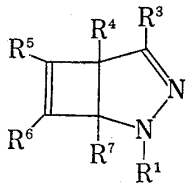
containing Methylene Blue or Rose Bengal as a sensitizer was irradiated with a high pessure mercury lamp for *ca.* 10 hr, during which time a steady stream of oxygen was bubbled through the solution. The photolysate was chromatographed over silica gel to give the 4,7-epidioxides (**2a**—**e**) as main products in 30—60% yields.



1 **2**

	R^1	R^3	R^4	R^5	R^6	R^7
a:	CO_2Et	H	H	H	H	H
b:	CO_2Et	Me	H	H	H	H
c:	CO_2Et	H	H	Me	H	H
d:	CO_2Et	H	Me	H	Me	H
e:	COMe	H	H	H	H	H



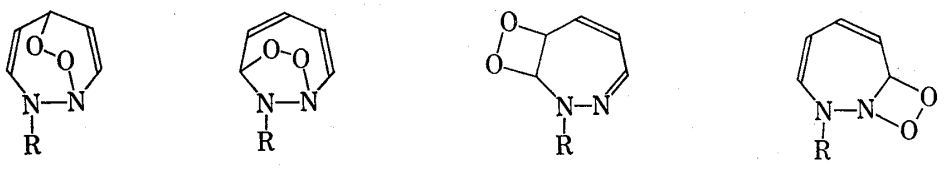
3

Chart 1

The products (**2**) gave analyses and mass spectra consistent with formulation as starting material plus one molecule of oxygen. The mass (MS) spectra have significant peaks at M-32 (loss of oxygen) and the nuclear magnetic resonarce (NMR) spectral data are closely analogous to those of the 4,7-cycloadducts of 1 with tetracyanoethylene[7a] and 4-phenyl-1,2,4-triazoline-3,5-dione.[10]

The bicyclic products (3a-e) were also obtained in *ca.* 5% yields, besides the dioxides (**2**). Direct formation of **3** from **1** by irradiation has been already reported[11] and structures of **3** were confirmed by comparison with the reported data. However, any other possible dioxides and their decomposition products were not isolated from the reaction mixture. This photo-oxygenation was negligible in the absence of a sensitizer.

These results show that the epidioxides (**2**) are the sole adducts and the other possible adducts, *e.g.*, epidioxides (**4** and **5**) and oxetanes (**6** and **7**), are not formed by this oxygenation. Thus, the oxygenation of the diazepines proceeds through $(4+2)\pi$ cycloaddition of a singlet oxygen as a high-energy dienophile to the diene rather than to the aza-diene system, and does not involve $(6+2)\pi$ or $(2+2)\pi$ cycloaddition to the triene unit in contrast to the cases of cycloheptatrienes[3] and 1,3-oxazepines.[5]



4 **5** **6** **7**

Chart 2

10) T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc.* (*C*), **1971**, 2141.
11) J. Streith, J.P. Luttringer, and M. Nastasi, *J. Org. Chem.*, **36**, 2962 (1971).

It has been postulated that the oxygenation of cycloheptatrienes and oxazepines involves the initial formation of the corresponding dioxides which subsequently decompose to the products isolated. However, the dioxides have not been isolated and no direct evidence was available for the intermediacy of the dioxides. In connection with these facts, it seems interesting that the epidioxides (**2**) are isolated as stable crystals in the present work. The structures of **2** were further confirmed by the following chemical studies.

The dioxides (**2**) were readily reverted to the parent diazepines (**1**) with a loss of oxygen by passage through an alumina column or by treatment with triethylamine in methanol at room temperature.

Treatment of **2a—d** with potassium hydroxide in methanol under ice-cooling gave the epoxy-diazepinones (10a—d) in 30—60% yield. However, when **2a,d** in methanol were stirred at room temperature for several days without the base, the solvent adducts (**11a,d**) were formed in 60—65% yields.

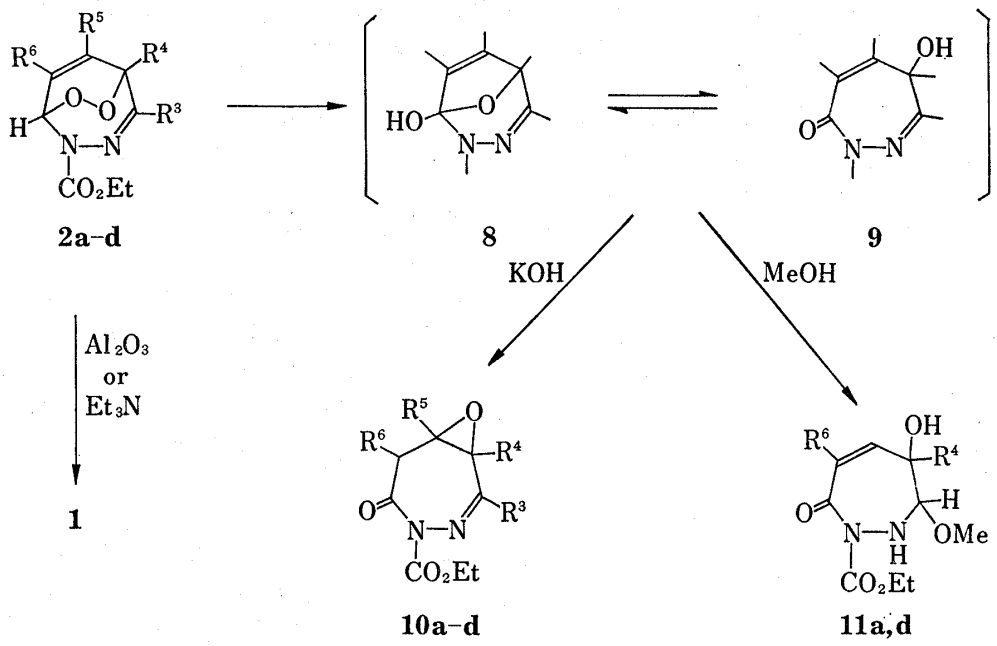


Chart 3

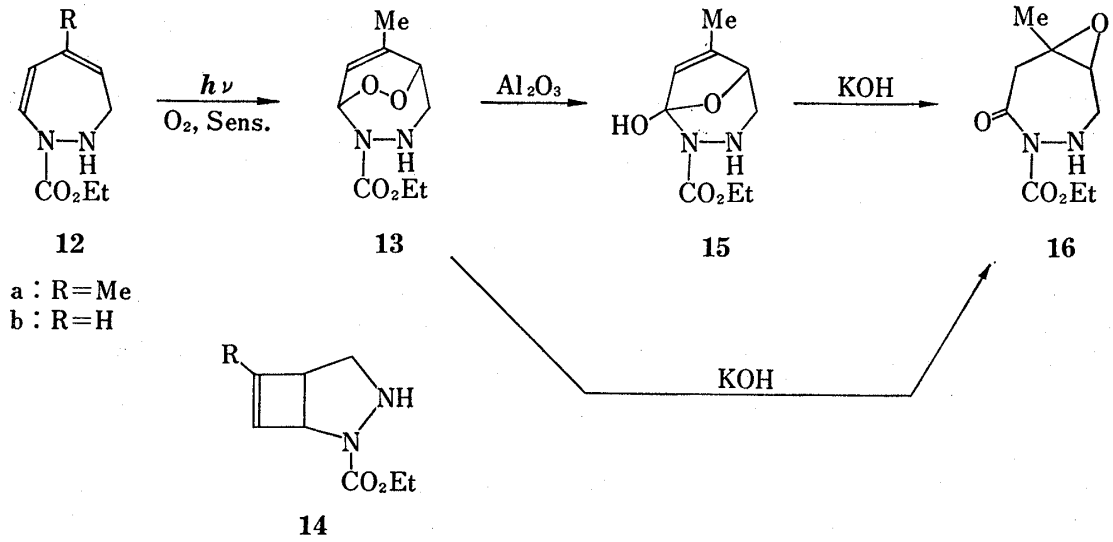


Chart 4

The base treatment of diene epidioxides with a proton α to the peroxy group has been known to result in the formation of the corresponding hydroxy-ketones and -epoxides by O–O bond fission.[12] Hence, the present base treatment may also involve initial formation of the intermediates (**8**) and (**9**), followed by isomerization to give the epoxides (**10**) in the basic condition and by solvent incorporation to give the hydroxides (**11**) in the neutral solution, as shown in Chart 3, although all attempts to isolate the intermediates failed. This mechanistic consideration may be supported by the following results, especially, conversion of **15** into **16**.

Similar photo-oxygenation of the 2,3-dihydro-1H-1,2-diazepine (**12a**), which was prepared from **1c** by sodium borohydride reduction,[13] gave the 4,7-epidioxides (**13**) in 73% yield along with the bicyclic product (**14**) in *ca.* 15% yield. In this case, no other possible dioxides have also been isolated in analogy with the case of **1**. The unsubstituted dihydrodiazepine (**12b**) gave only the bicyclic product (**14b**) in 30—35% yield and did not give the expected dioxide derivative, probably because of its instability.

The structure of **13** was confirmed by comparing its NMR spectral data with those of the 4,7-cycloadduct of **12** with 4-phenyl-1,2,4-triazoline-3,5-dione.[13] The direct photo-cyclization of **12** into **14** has also been reported.[13]

Treatment of **13** with alumina in methylene chloride resulted in the formation of the hydroxy-epoxide (**15**) as stable crystals in 80% yield. Further treatment of **15** with an alkali such as potassium hydroxide in methanol yielded almost quantitatively the epoxy-diazepinone (**16**), which was also obtained directly from **13** in 35% yield by treatment with an alkali. This result strongly supports the above-mentioned mechanistic proposal for the formatiom of **10** *via* the intermediate (**8**) by treatment with the base. However, no 7-hydroxydiazepin-4-one derivatives were obtained by treatment with bases or alcohols.

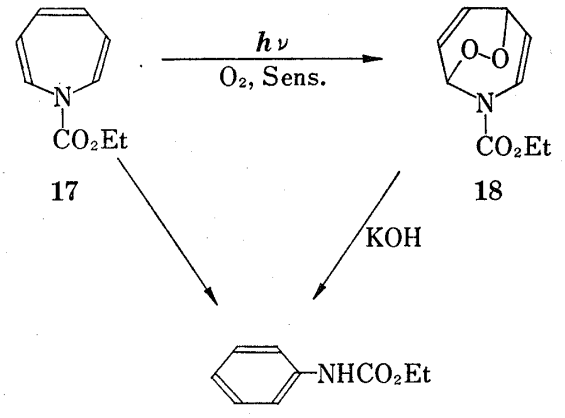


Chart 5

Similarly, 1-ethoxycarbonylazepine[14] (**17**) was photo-oxygenated to give the 2,5-epidioxide (**18**) in 70—75% yield as the sole dioxide product. Treatment of **18** with a base such as potassium hydroxide or sodium methoxide gave N-ethoxycarbonylaniline (**19**) in 60—70% yield and any expected epoxy compounds could not be isolated in contrast with the cases of **2** and **13**.

Formation of **19** may involve initial deoxygenation to the parent azepine followed by isomerization, which is supported by the fact that the azepine (**17**) readily isomerizes to **19** by treatment with the bases.

Experimental

Melting points were measured on a Yamato MP-1 apparatus and are uncorrected. Infrared (IR) spectra were determined with a JASCO IRA-1 spectrometer and MS spectra were obtained on Hitachi RMS-4 and JEOL JMS-D100 instruments. NMR spectra were recorded on Hitachi R-20 and R-22 spectrometers in $CDCl_3$ solution using tetramethylsilane as internal standard unless otherwise stated and spectral assignments

12) M. Oda and Y. Kitahara, *Chem. Lett.*, **1974**, 345; P.A. Burns, C.S. Foote, and S. Mazur, *J. Org. Chem.*, **41**, 899 (1976); and refs. cited therein.
13) T. Tsuchiya and V. Snieckus, *Can. J. Chem.*, **53**, 519 (1975).
14) K. Hafner, D. Zinser, and K.L. Moritz, *Tetrahedron Lett.*, **1964**, 1733.

were confirmed by spin-decoupling experiments and, in the case of NH and OH protons, by exchange with D_2O. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer in EtOH solution. Microanalyses were performed in the Microanalytical laboratory, Showa University, by Miss T. Kihara and Mrs. K. Shiobara.

Photolyses were carried out in an immersion apparatus equipped with a 100 W high-pressure Hg lamp, which was cooled internally with running water.

Photo-oxygenation of 1H-1,2-Diazepines (1a—e). Formation of 4,7-Epidioxides (2a—e)——General Procedure: A solution of **1** (1—2 g) in dry CH_2Cl_2 (200 ml) containing 50 mg of Methylene Blue or Rose Bengal was irradiated with a high-pressure Hg lamp using a Pyrex filter for *ca.* 10 hr, during which time a steady stream of oxygen was bubbled through the solution. After evaporation of the solvent *in vacuo*, the resulting residue was chromatographed over silica gel using benzene–AcOEt mixture as eluent to give the epidioxides (**2**). Usually, besides **2**, the bicyclic compounds (**3**) were also obtained in 5—10% yields.

2a: 50% yield, mp 103—104° [from isopropyl ether (IPE)]. MS *m/e*: 198 (M^+). UV λ_{max} nm (ε): 243 (6400). IR ν_{max}^{KBr} cm^{-1}: 1605, 1720. NMR δ: 1.36 and 4.34 (3H, t, and 2H, q, CO_2Et), 4.70 (1H, m, 4-H), 6.32 (1H, m, 6-H), 6.71 (1H, m, 5-H), 6.80 (1H, m, 7-H), 7.01 (1H, m, 3-H), $J_{3,4}=5.4$, $J_{4,5}=6.5$, $J_{4,6}=1.5$, $J_{4,7}=0.6$, $J_{5,6}=6.6$, $J_{5,7}=1$, $J_{6,7}=7.8$ Hz. *Anal.* Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.28; H, 5.10; N, 14.40.

2b: 45% yield, viscous oil. MS *m/e*: 212 (M^+). UV λ_{max} nm (ε): 244 (4800). IR ν_{max}^{film} cm^{-1}: 1610, 1720. NMR δ: 1.30 and 4.27 (3H, t, and 2H, q, CO_2Et), 2.10 (3H, s, 3-Me), 4.70 (1H, m, 4-H), 6.32 (1H, m, 6-H), 6.71 (1H, m, 5-H), 6.75 (1H, dd, 7-H). *Anal.* Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.11; H, 5.51; N, 13.42.

2c: 60% yield, viscous oil. MS *m/e*: 212 (M^+). UV λ_{max} nm (ε): 239 (5300). IR ν_{max}^{film} cm^{-1} 1603, 1720. NMR δ: 1.36 and 4.34 (3H, t, and 2H, q, CO_2Et), 2.04 (3H, d, $J=1.2$ Hz, 5-Me), 4.58 (1H, dd, 4-H), 6.03 (1H, m, 6-H), 6.75 (1H, d, 7-H), 7.04 (1H, d, 3-H). *Anal.* Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.78; H, 5.83; N, 13.42.

2d: 35% yield, mp 76—77° (from IPE). MS *m/e*: 226 (M^+). UV λ_{max} nm (ε): 236 (7100). IR ν_{max}^{KBr} cm^{-1}: 1603, 1720. NMR δ: 1.36 and 4.35 (3H, t, and 2H, q, CO_2Et), 1.41 (3H, s, 4-Me), 2.00 (3H, d, $J=1.5$ Hz, 6-Me), 6.10 (1H, br s, 5-H), 6.63 (1H, d, 7-H), 6.76 (1H, s, 3-H). *Anal.* Calcd. for $C_{10}H_{14}N_4O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.80; H, 6.51; N, 12.28.

2e: 50% yield, mp 76—78° (from IPE). MS *m/e*: 168 (M^+). UV λ_{max} nm (ε): 240 (5800). IR ν_{max}^{KBr} cm^{-1}: 1603, 1695. NMR δ: 2.31 (3H, s, COMe), 4.71 (1H, m, 4-H), 6.30 (1H, m, 6-H), 6.71 (1H, m, 5-H), 6.95 (1H, m, 7-H), 7.05 (1H, d, 3-H). *Anal.* Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.11; H, 5.02; N, 16.47.

Treatment of 2 with Triethylamine and Alumina——Triethylamine: A solution of **2** (*ca.* 100 mg) and triethylamine (1 g) in CH_2Cl_2 (20 ml) was stirred at room temperature overnight. The reaction mixture was evaporated and the residue was chromatographed over silica gel using benzene–AcOEt as eluent to give the starting diazepines (**1**) in *ca.* 80—85% yield.

Alumina: A solution of **2** (100 mg) in CH_2Cl_2 was passed through an active alumina column and the eluate was evaporated to dryness. The rseidue was chromatographed over silica gel to give **1** in 70—80% yield.

Reaction of 2a—d with KOH. Formation of the Epoxy-diazepinones (10a—d)——A mixture of **2** (300 mg) and an equivalent amount of KOH in MeOH cooled in an ice bath was stirred for 1 hr. After removing the alkali by passage through a silica gel column, the reaction mixture was evaporated to dryness. The residue was chromatographed over silica gel using benzene–AcOEt (4: 1) as eluent to give **10**, which was purified by recrystallization from acetone–ether mixture.

10a: 35% yield, mp 177—178°. MS *m/e*: 198 (M^+). UV λ_{max} nm (ε): 242 (9200). IR ν_{max}^{KBr} cm^{-1}: 1710, 1790. NMR δ: 1.33 and 4.28 (3H, t, and 2H, q, CO_2Et), 2.98 (2H, m, 6-H_2), 4.74 (1H, m, 5-H), 5.62 (1H, dd, 4-H), 7.09 (1H, br s, 3-H), $J_{3,4}=0.8$, $J_{4,5}=8$, $J_{6,6}=19$ Hz. *Anal.* Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.59; H, 5.37; N, 14.01.

10b: 45% yield, mp 114—115°. MS *m/e*: 211 (M^+). UV λ_{max} nm (ε): 240 (9300). IR ν_{max}^{KBr} cm^{-1}: 1710, 1785. NMR δ: 1.35 and 4.30 (3H, t, and 2H, q, CO_2Et), 2.19 (3H, s, 3-Me), 3.00 (2H, m, 6-H_2), 4.84 (1H, m, 5-H), 5.54 (1H, d, 4-H). *Anal.* Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.13; H, 5.59; N, 13.38.

10c: 40% yield, mp 78—79°. MS *m/e*: 212 (M^+). UV λ_{max} nm (ε): 242 (8700). IR ν_{max}^{KBr} cm^{-1}: 1700, 1790. NMR δ: 1.38 and 4.34 (3H, t, and 2H, q, CO_2Et), 1.36 (3H, s, 5-Me), 2.81 and 3.45 (1H, d, and 1H, d, 6-H_2), 5.16 (1H, d, 4-H), 7.09 (1H, br s, 3-H). *Anal.* Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.72; H, 5.81; N, 13.50.

10d: 55% yield, mp 102—103°. MS *m/e*: 226 (M^+), UV λ_{max} nm (ε): 240 (8800). IR ν_{max}^{KBr} cm^{-1}: 1695, 1785. NMR δ: 1.33 and 4.00 (3H, t, and 2H, q, CO_2Et), 1.49 (3H, d, $J=8$ Hz, 6-Me), 1.67 (3H, s, 4-Me), 2.91 (1H, dq, 6-H), 4.02 (1H, d, 5-H), 6.89 (1H, s, 3-H). *Anal.* Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.38; H, 6.20, N, 12.29.

Methanolysis of 2a, d. Formation of the Hydroxy-diazepinones (11)——A solution of **2** (200 mg) in MeOH (20 ml) was stirred at room temperature for 2—3 days and the solution was evaporated to dryness *in vacuo*.

The resulting residue was chromatographed over silica gel using benzene–AcOEt (1: 1) as eluent to give **11**.

11a: 65% yield, mp 90—92°. MS *m/e*: 230 (M^+). UV λ_{max} nm (ε): 222 (13000). IR ν_{max}^{KBr} cm^{-1}: 1750, 3370. NMR (acetone-d_6) δ: 1.33 and 4.30 (3H, t, and 2H, q, CO_2Et), 2.92 (1H, br, OH), 3.50 (3H, s, OMe), 4.09 (1H, dd, 3-H), 4.53 (1H, m, 4-H), 5.35 (1H, br, NH), 5.92 (1H, dd, 6-H), 6.51 (1H, dd, 5-H), $J_{2,3}$=2, $J_{3,4}$=7.2, $J_{4,5}$=3.6, $J_{5,6}$=12 Hz. *Anal.* Calcd. for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 46.86; H, 6.26; N, 12.03.

11d: 60% yield, mp 135—137° (from acetone). MS *m/e*: 258 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1720, 3300. NMR (acetone-d_6) δ: 1.30 and 4.22 (3H, t, and 2H, q, CO_2Et), 1.38 (3H, s, 4-Me), 1.95 (3H, d, J=1 Hz, 6-Me), 3.80 (1H, br, OH), 4.32 (1H, br s, 3-H), 6.10 (1H, m, 5-H), 6.28 (1H, br, NH). *Anal.* Calcd. for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.03; N, 10.85. Found: C, 51.27; H, 7.30; N, 10.66.

Photo-oxygenation of 1-Ethoxycarbonyl-5-methyl-2,3-dihydro-1H-1,2-diazepine (12). Formation of the 4,7-Epidioxide (13)——A solution of **12** (1 g) and Methylene Blue (40 mg) in CH_2Cl_2 (200 ml) was irradiated and worked up similarly to the procedure described for **1** to give **13**: *ca.* 70% yield, mp 87—88° (from ether). MS *m/e*: 214 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1690, 3280. NMR δ: 1.29 and 4.23 (3H, t, and 2H, q, CO_2Et), 2.00 (3H, d, 5-Me), 3.13 and 3.46 (1H, dd, and 1H, dd, 3-H_2), 3.96 (1H, br d, 2-H), 4.58 (1H, m, 4-H), 6.07 (1H, br d, 6-H), 6.39 (1H, d, 7-H), $J_{3,3'}$=15, $J_{2,3}$=10, $J_{3,4}$=4, $J_{5,6}$=2, $J_{6,7}$=7 Hz. *Anal.* Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.32; H, 6.69; N, 13.28.

Treatment of 13 with Alumina. Formation of the Hydroxy-epoxide (15)——A solution of **13** (1 g) in CH_2Cl_2 was passed through an alumina column and the eluate was evaporated *in vacuo*. The resulting residue was chromatographed over silica gel using benzene–AcOEt (1: 1) as eluent to give **15**: 80% yield, viscous oil. MS *m/e*: 214 (M^+). IR ν_{max}^{film} cm^{-1}: 1740, 3330, 3440. NMR δ: 1.26 and 4.19 (3H, t, and 2H, q, CO_2Et), 2.14 (3H, br s, 5-Me), 3.08 and 3.41 (1H, dd, and 1H, dd, 3-H_2), 4.20 (1H, br, NH), 5.01 (1H, m, 4-H), 5.88 (1H, m, 6-H), 6.80 (1H, br, OH), $J_{3,3'}$=13, $J_{3,4}$=6.4 and 3 Hz. *Anal.* Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.73; H, 6.38; N, 13.11.

Treatment of 15 with KOH. Formation of the Epoxy-diazepinone (16)——A mixture of **15** (500 mg), KOH (50 mg), and MeOH (20 ml) cooled in an ice bath was stirred for 2 hr. After removing the alkali by passage through an alumina column, the reaction solution was evaporated to dryness *in vacuo* at room temperature. The residue was chromatographed over silica gel using benzene–AcOEt as eluent to give **16**: quantitative yield, viscous oil. MS *m/e*: 214 (M^+). IR ν_{max}^{film} cm^{-1}: 1690, 1780, 3240 cm^{-1}. NMR δ: 1.32 and 4.21 (3H, t, and 2H, q, CO_2Et), 1.67 (3H, s, 5-Me), 2.72 and 3.28 (1H, d, and 1H, d, 6-H_2), 3.19 and 3.38 (1H, d, and 1H, d, 6-H_2), 3.19 and 3.38 (1H, d, and 1H, d, 3-H_2), 3.74 (1H, s, 4-H), 4.83 (1H, br, NH), $J_{3,3'}$= 14, $J_{6,6'}$=18 Hz. *Anal.* Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.41; H, 6.71; N, 13.32.

The compound (**16**) was also obtained directly from **13** by treatment with KOH similar to the case of **15** in *ca.* 35% yield.

Photo-oxygenation of 1-Ethoxycarbonylazepine (17). Formation of the 2,5-Epidioxide (18)——A solution of **17** (1 g) and Methylene Blue (40 mg) in $CHCl_2$ (200 ml) was irradiated and worked up similarly to the procedure described for **1** to give **18**: 75% yield, viscous oil. MS *m/e*: 197 (M^+). UV λ_{max} nm (ε): 249 (6700). IR ν_{max}^{film} cm^{-1}: 1640, 1725. NMR δ: 1.31 and 4.24 (3H, t, and 2H, q, CO_2Et), 4.60 (1H, dd, 5-H), 5.22 (1H, t, 6-H), 6.11 (1H, dd, 3-H), 6.69 (1H, br d, 2-H), 6.72 (1H, m, 4-H), 6.79 (1H, br d, 7-H), $J_{2,3}$=7, $J_{3,4}$=8, $J_{3,5}$=1, $J_{4,5}$=6, $J_{5,6}$=8, $J_{6,7}$=8 Hz. *Anal.* Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.56; H, 5.55; N, 7.21.

Treatment of 18 with KOH——A mixture of **18** (350 mg) and KOH (90 mg) in MeOH was worked up quite similarly to the procedure for **2**. From the eluate with AcOEt, N-ethoxycarbonylaniline (**19**): mp 50—51° (lit.[15] 50—51°) was obtained in 60% yield.

15) T. Curtius, *J. Pract. Chem.*, **52**, 210 (1895).