Studies on Diazepines. X.¹⁾ The Sensitized Photo-oxygenation of 1H-1,2-Benzodiazepines

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The photosensitized oxygenation of 1H-1,2-benzodiazepines (6) in methanol gave fragment products (7—14). Phenyl ketones (7) are assumed to originate from the 5-hydroperoxide (5), and cinnamic acids (8 and 9), 3-methoxy-3H-1,2-benzodiazepines (10), and indazoles (11—14) from the 3-hydroperoxide (16). Similar photooxygenation of 1-methyl-1H-1,2-benzodiazepines (23) gave 3-oxo-1,2-benzodiazepines (25), which may be formed *via* the zwitterionic 3-peroxide (24).

Keywords—1H-1,2-benzodiazepines; photo-oxygenation; sensitized photooxygenation hydroperoxide; mechanism

In view of the interesting photosensitized oxygenation behavior of seven-membered conjugated trienes such as cycloheptatrienes (tropilidenes)³⁾ and tropolones,⁴⁾ we have been examining similar reactions of aza-analogs, and we have already reported that the photo-oxygenation of the monocyclic azepines (1) and 1,2-diazepines (2) yields the relatively stable (4 π +2 π) cycloadducts (3) and (4) as the sole oxidized products.⁵⁾ On the other hand, 2-phenyl-1,3-oxazepine (5) was shown to undergo initial 1,2- (or 1,6-) and 1,4-addition of singlet oxygen, followed by decomposition to give several oxidized fragments.⁶⁾ In all cases of the aza-cycloheptatrienes (1, 2, and 5), 1,2- and 1,4-cycloadditions of oxygen did not occur in the aza-diene system. However, it has been shown that the oxygenation of imidazoles and xanthines involves 1,4-cycloaddition of singlet oxygen at the aza-diene function,⁷⁾ and the attack of oxygen occurs at both the double bond and benzene ring in the case of indenenes.⁸⁾

Chart 1

In connection with the above-mentioned studies, we examined the photooxygenation of 1H-1,2-benzodiazepines (6 and 23), which were expected to produce different types of

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oxidized products compared to those obtained in the oxygenation of **2** and **5** because of the presence of the benzene ring. We report here evidence that the main pathway may proceed through an ene reaction of singlet oxygen and not through cycloaddition.⁹⁾

A methanol solution of 1H-1,2-benzodiazepine (**6a**)¹⁰⁾ was photooxygenated for 2 hr with a halogen lamp using Rose Bengal or Methylene Blue as a sensitizer while oxygen was slowly passed through the solution. After removal of the solvent, the photolysate was chromatographed on silica gel to give benzaldehyde (**7a**: ca. 20%), cinnamic acid (**8a**: 12%), methyl cinnamate (**9a**: 18%), 3-methoxy-3H-1,2-benzodiazepine¹¹⁾ (**10a**: 6%), 3-formylindazole¹²⁾ (**11**: 3%), and 3-(*trans*-2'-methoxyvinyl)-1H-indazole¹⁾ (**13**: 4%). In a similar manner, 5-methyl-1H-1,2-benzodiazepine¹⁰⁾ (**6b**) gave acetophenone (**7b**: 28%), β -methylcinnamic acid (**8b**: 20%), methyl β -methylcinnamate (**9b**: 11%), 3-methoxy-5-methyl-3H-1,2-benzodiazepine¹¹⁾ (**10b**: 2%), 3-methylindazole¹³⁾ (**12**: 3%), and 3-methyl-3-(*trans*-2'-methoxyvinyl)-3H-indazole¹⁾ (**14**: 5%), as shown in Chart 2.¹⁴⁾

Chart 2

When methylene chloride was used as a solvent instead of methanol in the reaction, the photolysate decomposed with evolution of oxygen during concentration, and gave only the phenyl ketones (**7**: 15–20%) without any other characterizable products. Photooxygenation was negligible in the absence of a sensitizer.

In order to examine the relationships among these products, each of them was further photooxygenated under conditions similar to those used for their formation. The phenyl ketones (**7**) were not obtained by photooxygenation of the cinnamic acids (**8** and **9**) or any other products, suggesting that the ketones are not secondarily formed from the other isolated

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- 14) All the products isolated are known and their identities were confirmed by comparison with authentic samples purchased or prepared according to the literature.

Chart 3

products. The 3H-indazole (**14**) was converted into 3-methyl-1H-indazole (**12**), whereas oxygenation of the 1H-indazole (**13**) did not give **11**. The reaction of the 3H-diazepines (**10**) resulted in the formation of indazoles **11** and **13** or **12** and **14**. These results suggest that the photooxygenation of the diazepines (**6**) may involve the initial formation of two different oxidized intermediates; one may be unstable and may readily decompose to give **7**, while the other is more stable and reacts with methanol followed by decomposition to give the products (**8–14**).

Based on these results and observations, the present photooxygenation can be accounted for by the scheme outlined in Chart 3. Although all attempts to isolate the key intermediates **15** and **16** failed, we believe that the reaction involves the initial formation of 5- (**15**) and 3- (**16**) hydroperoxides, followed by isomerization and/or decomposition to give the fragmental products. Since the 5H-1,2-benzodiazepines are known¹⁵⁾ to be unstable, the 5-hydroperoxides (**15**) may be decomposed to give the phenyl ketones (**7**) by $\text{C}_4\text{—C}_5$ bond cleavage and loss of nitrogen. On the other hand, 3H-1,2-benzodiazepines are known¹¹⁾ to be relatively stable but to undergo both photochemical and thermal rearrangements to the corresponding 3-vinylindazoles in high yields. Therefore, the 3-peroxides (**16**) may rearrange into the 3H-indazoles (**14** and **17**) *via* **10** or **18**, followed by further oxygenation of the olefinic double bond to give the formylindazoles (**19**), which are then converted into either **11** or **12**. Cinnamic acids (**8**) and cinnamates (**9**) may also result from **16** *via* the 3H-indazoles (**22**), which are formed either *via* the 3-oxodiazepines (**20**) and the ketene intermediates (**21**), or *via* the peroxides (**18**).

Next, methanol solutions of 1-methyl-1H-1,2-benzodiazepines (**23a, b**), prepared from **6** by treatment with *n*-butyl lithium followed by methyl iodide in tetrahydrofuran, were photooxygenated under similar conditions to give the 3-oxo-benzodiazepines (**25**) in 60–65% yields

15) T. Tsuchiya and J. Kurita, presented at the 47th Meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Toyama, Nov., 1978.

Chart 4

as the sole products.¹⁶⁾ In these cases, other possible dioxides and their decomposition products could not be isolated. This reaction may involve the initial formation of the zwitterionic 3-peroxides (24) analogous to those observed for enamines¹⁷⁾ with no formation of 5-peroxides.

In conclusion, it should be noted that no product derived from the other possible dioxides such as the 4,5- (26), 2,5- (27), 4,7- (28), or 2,7- (29) dioxide has been detected.¹⁸⁾ Thus, in the present photooxygenation of the 1H-1,2-benzodiazepines (6 and 23), the formation of hydroperoxides occurs predominantly, and 1,4-, 1,6-, and 1,2- cycloadditions of singlet oxygen do not occur either in the aza-diene system or the diene involved in the benzene ring.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Infra red (IR) spectra were determined with a JASCO IRA-2 spectrometer and Mass (MS) spectra were obtained on a JEOL JMS-D100 instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-MH100 spectrometer in CDCl₃ 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 D₂O. Microanalyses were performed in the Microanalytical Laboratory of this school by Miss R. Hamano. Photolyses were carried out using an immersion apparatus equipped with a halogen lamp (Ushio JCV-200W-GS) which was cooled internally with running water.

Photooxygenation of 1H-1,2-Benzodiazepine (6a)—A solution of 6a (3.0 g) in methanol (300 ml) containing Rose Bengal or Methylene Blue (50—100 mg) was irradiated with a halogen lamp for 2 hr while a steady stream of oxygen was bubbled through the solution. After removal of the solvent *in vacuo*, the residue was dissolved in CH₂Cl₂ and the solution was extracted with satd. NaHCO₃. The alkaline solution was acidified with 10% HCl and extracted with ether. The extract was washed with water, dried over MgSO₄, and evaporated to dryness. The resulting solid was recrystallized from AcOEt to give cinnamic acid (8a: 360 mg, 12%). The above CH₂Cl₂ solution was washed with satd. NaCl, dried, and evaporated to dryness *in vacuo*. The resulting residue was chromatographed on silica gel using *n*-hexane-CH₂Cl₂ as an eluent to give benzaldehyde (7a: 440 mg, 20%), methyl cinnamate (9a: 620 mg, 18%), 3-methoxy-3H-1,2-benzodiazepine (10a: 210 mg, 6%, mp 53—54°), 3-formyl-1H-indazole (11: 57 mg, 2%), and 3-(*trans*-2'-methoxyvinyl)-1H-indazole (13: 140 mg, 4%, mp 82—84°), successively. The compounds 10a¹¹⁾ and 13¹⁾ were identical

16) These products (25) are the first examples of 3-oxo-1,2-diazepines.

17) For a review, see I. Saito, T. Matsuura, M. Nakagawa, and T. Hino, *Acc. Chem. Res.*, **10**, 346 (1977).

18) Although other routes for the formation of 7 from 6 *via* 26 or 27 can be considered, these routes seem unlikely based on the results of oxygenation of 23.

with the authentic samples reported in our previous papers. An authentic sample of **11** was prepared by the reported method¹²⁾ and authentic samples of the other products were obtained from Tokyo Kasei Kogyo Co., Ltd, Tokyo, Japan.

Photooxygenation of 5-Methyl-1H-1,2-benzodiazepine (6b)—A solution of **6b** (3.0 g) in methanol (300 ml) containing Rose Bengal (100 mg) was photooxygenated for 4.5 hr and worked up as described for **6a** to give β -methylcinnamic acid (**8b**: 75 mg, 2%), acetophenone (**7b**: 640 mg, 28%), methyl β -methylcinnamate (**9b**: 360 mg, 11%), 3-methoxy-5-methyl-3H-1,2-benzodiazepine¹¹⁾ (**10b**: 80 mg, 2%, yellow viscous oil), 5-methyl-3-(*trans*-2'-methoxyvinyl)-3H-indazole¹⁾ (**14**: 180 mg, 5%, colorless viscous oil), and 3-methyl-1H-indazole (**12**: 70 mg, 3%). Authentic samples of the products **7b**, **8b**, and **9b** were obtained from Tokyo Kasei Kogyo Co., Ltd. and authentic samples of the other products (**10b**, **12**, and **14**) were prepared by the reported methods.

Preparation of 1-Methyl-1H-1,2-benzodiazepines (23a, b)—A solution of *n*-butyl lithium (15% w/w in *n*-hexane, $d=0.68$, 24 ml) was added dropwise to a solution of **23** (5.0 g) in anhydrous tetrahydrofuran cooled in a dry ice-acetone bath with stirring under a nitrogen atmosphere, then a solution of methyl iodide (5.4 g) in tetrahydrofuran (10 ml) was further added dropwise to the reaction solution. After stirring for an additional 30 min at -50 — -60° , the reaction mixture was warmed to room temperature and water (50 ml) was added. The mixture was extracted with CH_2Cl_2 and the extract was washed with water, dried, and evaporated to dryness *in vacuo*. The resulting residue was chromatographed on silica gel, eluting with *n*-hexane- CH_2Cl_2 , to give **23**.

23a: 3.59 g, 68% yield, mp 61 — 62° , red prisms (from *n*-hexane). MS m/e : 158 (M^+). NMR δ : 3.24 (3H, s, N-Me), 6.12 (1H, dd, $J=11$ and 4 Hz, 4-H), 6.9—7.5 (6H, unassigned m, 3-, 5-, and Ar-H). Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.78; H, 6.33; N, 17.60.

23b: 4.47 g, 86% yield, yellow oil, bp (bath temp.) 109° (3 mmHg). MS m/e : 172 (M^+). NMR δ : 2.23 (3H, br, 5-Me), 6.12 (1H, m, 4-H), 3.22 (3H, s, N-Me), 6.9—7.5 (5H, unassigned m, 3- and Ar-H). Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.61; H, 7.13; N, 16.07.

Photooxygenation of 23a—A solution of **23a** (1.0 g) in methanol (300 ml) containing Methylene Blue (100 mg) was irradiated with a halogen lamp for 5 hr while a steady stream of oxygen was bubbled through the solution. After removal of the solvent *in vacuo*, the resulting residue was chromatographed on silica gel using acetone- CH_2Cl_2 as an eluent to give 1-methoxy-3-oxo-1,2-dihydro-1,2-benzodiazepine (**25a**): 640 mg, 60% yield, mp 170 — 172° , colorless prisms (from AcOEt). MS m/e : 174 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2850—3200 (NH), 1660 (C=O). NMR δ : 3.12 (3H, s, N-Me), 6.23 (1H, d, 4-H), 6.99 (1H, d, 5-H), 6.9—7.4 (4H, m, Ar-H), 8.4 (1H, br NH), $J_{4,5}=11$ 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, 68.94; H, 5.78; N, 16.05.

Photooxygenation of 23b—A solution of **23b** (1.0 g) in methanol (300 ml) containing Methylene Blue (200 mg) was irradiated for 40 hr and worked up as described for **23a** to give 1,5-dimethyl-3-oxo-1,2-dihydro-1,2-benzodiazepine (**25b**): 706 mg, 65% yield, mp 201 — 203° , colorless needles (from AcOEt). MS m/e : 188 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2850—3200 (NH), 1670 (C=O). NMR δ : 2.25 (3H, br, 5-Me), 3.09 (3H, s, N-Me), 6.25 (1H, m, 4-H), 7.0—7.5 (4H, m, Ar-H), 9.0 (1H, br, NH). 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, 70.11; H, 6.44; N, 14.88.