Quinazolines and 1,4-Benzodiazepines. XLVI. (1) Photochemistry of Nitrones and Oxaziridines

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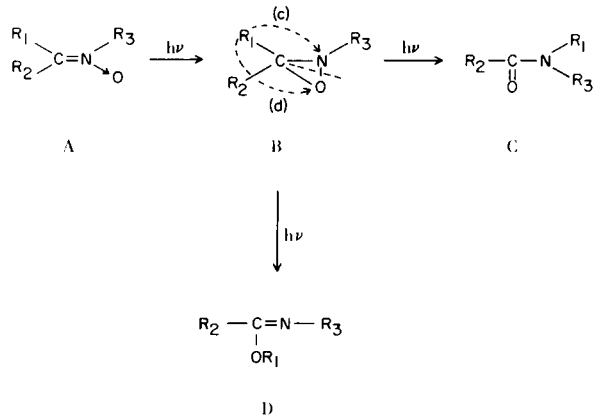
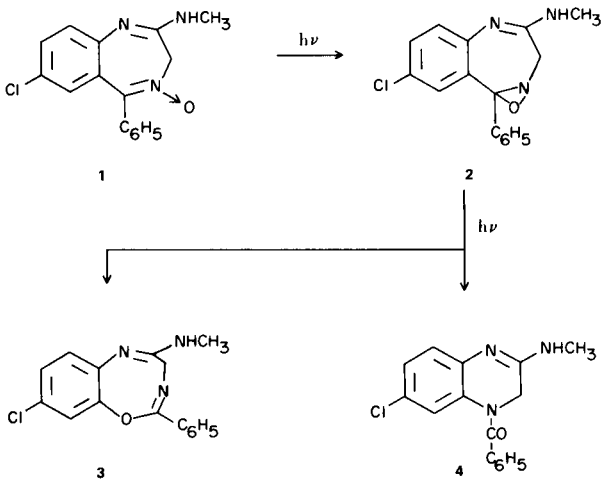
The cyclic nitrones 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**5a**) and 1,3-dihydro-7-methylthio-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**5b**) are photoisomerized to readily isolable oxaziridines, 7-chloro-4,5-epoxy-5-phenyl-1,3,4-5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**6a**) and 4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-7-methylthio-2*H*-1,4-benzodiazepin-2-one (**6b**). Oxaziridine **6b** upon further irradiation gave ring expansion and ring contraction products, 4,6-dihydro-2-phenyl-9-methylthio-5*H*-1,3,6-benzoxadiazocin-5-one (**7b**) and 4-benzoyl-3,4-dihydro-6-methylthioquinoxalin-2(1*H*)-one (**8b**) respectively. The ring contraction product, 4-benzoyl-6-chloro-3,4-dihydroquinoxalin-2(1*H*)-one (**8a**), was obtained from irradiation of oxaziridine **6a**.

Nitrones readily photoisomerize to oxaziridines (2) which are labile species and readily undergo additional transformations. Further irradiation frequently gives amides, which result from the cleavage of the N-O bond accompanied by the migration of a group (H, alkyl or aryl) from the carbon to the nitrogen of the three membered ring (3,4) as indicated by A → B → C.

Recently it has been reported that the irradiation of certain aromatic *N*-oxides results in ring enlargement and formation of oxygen containing heterocycles (7,8). Oxaziridines are postulated as intermediates, which then undergo a rearrangement which can be formally represented as

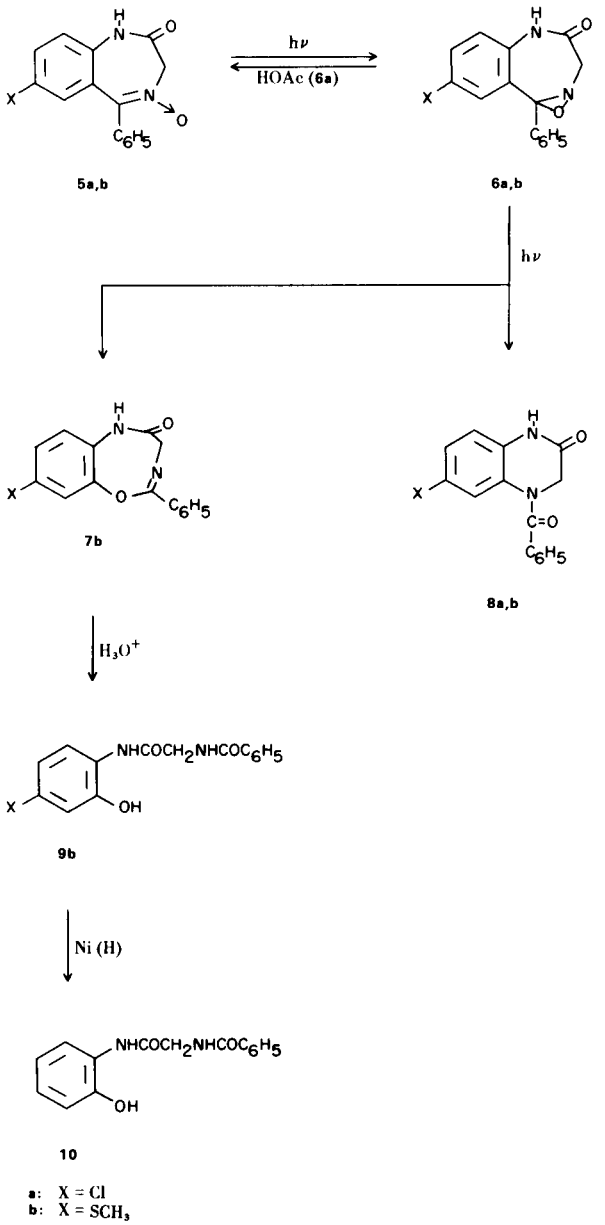


a cleavage of the N-O bond accompanied by migration of a group from the carbon to the oxygen of the three membered ring (B → D). In our laboratories, the photoisomerization of the 1,4-benzodiazepin-4-oxide **1** was studied (9). It yielded, *via* the intermediate oxaziridine **2** the benzoxadiazocine **3** and quinoxaline **4**. The conversions **2** → **3** and **2** → **4** are examples of the two types of rearrangements just mentioned. Since the ready isomerization of **1** to **3** is an interesting example of the occurrence of such a reaction in a nonaromatic system, we were induced to extend our study to systems represented by the lactam **5**. We have found that compounds of type **5** under go analogous reactions.



The oxaziridine **6a** used in these studies was prepared in 78% yield by irradiation of a tetrahydrofuran solution of 7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one 4-oxide (**5a**) (10) with a Hanovia medium-pressure mercury lamp and a Pyrex filter. The structure of this compound was indicated by the disappearance of the nitrone type of chromophore in the ultraviolet, and the ability to

oxidize iodide ions (2). Further evidence was the reversion to **5a** by treatment of **6a** with glacial acetic acid at room temperature. Prolonged irradiation of the solution of **6a** in tetrahydrofuran with Pyrex filtered light caused little change. Complete photolysis of **6a** required irradiation without a Pyrex filter which gave a complex product mixture from which only the ring contraction product **8a** (9a, 11) could be isolated.



Irradiation of the methylthio substituted nitrone **5b** (12) with Pyrex filtered light also gave a high yield of the oxaziridine **6b** (82%). This oxaziridine, in contrast to **6a**, was quite sensitive to prolonged irradiation. Pyrex filtered light caused rearrangement of **6b** to a mixture (approximately 1:3) of **7b** and **8b**, which was isolated in 65% yield. Pure **7b** was obtained as colorless needles (m.p. 202-203°) by fraction crystallization. It absorbed in the infrared at 3160, 1680 and 1660 cm^{-1}, suggesting the presence of NH, CO and C=N functions. In addition to absorption due to substituted phenyl rings, the ultraviolet absorption at 247 mμ (ε 23,300) may be assigned to the C_6H_5-C=N grouping. The high resolution mass spectrum of **7b** showed major ions with elemental compositions of $C_{16}H_{14}N_2O_2S$, $C_{14}H_{12}NOS$, $C_9H_9NO_2S$, C_8H_9NOS and C_8H_8NOS.

Pure **8b** (m.p. 242-243°) was isolated after hydrolysis of the contaminating **7b** to the more readily separable phenol **9b**. The high resolution mass spectrum of **8b** contained major ions with elemental compositions of $C_9H_8N_2OS$ (m-106) and C_7H_5O, indicating the loss of the *N*-benzoyl group, also a prominent feature in the fragmentation of **8a**. In addition, the infrared spectrum of **8b** was almost superimposable on that of **8a**, and the respective NMR spectra are also in good agreement.

The phenol **9b** was desulfurized with Raney nickel to the known compound **10** (9a, 12).

The fact that the ring expansion product **7b** was isolated on photolysis of **6b** makes it appear that the presence of a 1,2-double bond in these systems, such as found in **1**, is not necessary for the occurrence of oxygen insertion reactions.

EXPERIMENTAL

All melting points were taken in a Thomas-Hoover melting point apparatus, and were corrected. Ir spectra were determined using a Beckmann IR-9 or a Perkin-Elmer 621 grating spectrophotomer, ms with a CEC-21-110 spectrometer, nmr spectra with a Varian A-60 spectrometer using tetramethylsilane as internal standard and uv spectra with a Cary 14M or 15 recording spectrophotometer. All solvents used were of reagent grade purity. Unless otherwise specified, all solvents were evaporated on a Buchi Rotavapor evaporator, under water-aspirator pressure using a water bath set at 35-40°.

All photochemical reactions were conducted under nitrogen in a vessel surrounding a water-jacketed quartz well, which contained a Hanovia 250 W medium pressure mercury lamp (No. 654A). The Pyrex filters, when used, were Pyrex 7740 filter sleeves supplied by Hanovia.

1,3-Dihydro-7-methylthio-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**5b**) (12).

Procedures described in the patents cited were followed in preparing this compound, m.p. 193-194°, after recrystallization from acetone. UV max (ethanol), 245 mμ, (ε 24,000), 270 (28,600) and 310 (9500).

7-Chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**6a**).

A solution of 26.8 g. (93.5 mmoles) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**5a**) (10) in 1.4 l. of tetrahydrofuran was irradiated through a Pyrex filter at 20° for

22 hours. The solution was concentrated to a small volume. Addition of hexane and chilling gave 21.0 g. (78.5%) of **6a** as colorless prisms, melting with sudden decomposition in the temperature range of 136-150°. An analytical sample was prepared by recrystallization from tetrahydrofuran-methanol mixtures, m.p. 136° dec., IR (potassium bromide), 1690 cm^{-1}; UV max, (ethanol), 249 mμ (ε 13,150) and 292 (shoulder, 1600).

In the presence of glacial acetic acid the oxazirane **6a** gave a strongly positive starch-iodide test (2).

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.87; N, 9.77; Cl, 12.36. Found: C, 63.10; H, 3.62; N, 9.58; Cl, 12.05.

Isomerization of **6a** to **5a**.

A solution of 500 mg. (1.75 mmoles) of **6a** in 75 ml. of glacial acetic acid was allowed to stand at room temperature for 8 days. The acetic acid was evaporated. The residual gum on trituration with ether gave 397 mg. of crude **5a**, m.p. 230-232° dec. After recrystallizations from ethanol, the yield was 248 mg. (49.4%) of colorless plates, m.p. 236-237° dec., identical with authentic **5a** by TLC and IR.

4,5-Epoxy-5-phenyl-1,3,4,5-tetrahydro-7-methylthio-2*H*-1,4-benzodiazepin-2-one (**6b**).

A solution of 500 mg. of **5b** in 150 ml. of tetrahydrofuran was irradiated through a Pyrex filter. After 15 minutes (14) of irradiation the solution was concentrated at room temperature to a small volume. Addition of hexane caused crystallization of **6b**. After one recrystallization, by solution in a small volume of tetrahydrofuran at room temperature and addition of hexane, 410 mg. (82%) of pure **6b** was obtained as a colorless amorphous solid, m.p. 128.5° dec.; IR (potassium bromide), 1690 cm^{-1}; UV max (ethanol), 273 mμ (ε 16,200) and 366 (600). Starch-iodide test was positive.

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.89; H, 4.78; N, 9.47.

4-Benzoyl-6-chloro-3,4-dihydroquinoxalin-2(1*H*)-one (**8a**).

A solution of 5.00 g. of oxaziridine **6a** in 1.5 l. of tetrahydrofuran was irradiated without a filter. After 41 hours the oxaziridine had disappeared as indicated by TLC. The solvent was evaporated. The residual mixture upon crystallization from ethanol gave, in two crops, 1.54 g. of **8a** as a yellow solid, m.p. 245-247° dec. After recrystallization from ethanol, platelets were obtained, m.p. 255-257° [lit. (11) 255-257°]. It was identical with a synthetic sample (11) (mixture MP, TLC and IR).

4,6-Dihydro-2-phenyl-9-methylthio-5*H*-1,3,6-benzoxadiazocin-5-one (**7b**) and 4-Benzoyl-3,4-dihydro-6-methylthioquinoxalin-2(1*H*)-one (**8b**).

A solution of 1.00 g. (3.36 mmoles) of **5b** in 150 ml. of tetrahydrofuran was irradiated for 44 hours through a Pyrex filter. During this time, periodic assay by TLC showed that the initially formed oxazirane **6b** disappeared gradually and that compounds **7b** and **8b** were formed, along with unknown materials having much lower Rf values on TLC (15). The crude solution which gave a negative starch-iodide test was concentrated. The gummy residue was crystallized from benzene and yielded 652 mg. (65%) of an amorphous, slightly yellow solid, which (by TLC analysis) contained only **7b** and **8b**.

Recrystallization gave a mixture of colorless needles and flakes, the former being the ring expansion product **7b** and the latter the ring contraction product **8b**. By fractional recrystallization from ethanol, compound **7b** was isolated in pure form, m.p. 202-203°, (24 mg.; 2.4%) (16). Pure **8b** was obtained from the second and third crops by destruction of compound **7b** by heating the mixture *in vacuo* (0.03 mm) to 180-184° for 15 minutes, followed by recrystallization from ethanol. It forms colorless flakes, m.p. 242-243° (160 mg.; 16%) (16). Compound **7b**; IR (potassium bromide) 3160 cm^{-1} (NH), 1680 (C=O) and 1660 (shoulder, C=N); uv max (ethanol), 238 mμ (sh) (ε 22,350), 247 (23,300, C_6H_5-C=N), 262 (21,800) and 305 (sh) (2710); mass spectrum (high resolution, major ions) (17) m/e 298 ($C_{16}H_{14}N_2O_2S$), 242 ($C_{14}H_{12}NOS$), 195 ($C_9H_9NO_2S$), 167 (C_8H_9NOS) and 166 (C_8H_8NOS).

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.24; H, 4.92; N, 9.36.

Compound **8b**.

IR (potassium bromide), 3200 cm^{-1} (NH), 1680 (NHCO) and 1650 (=N-CO); uv max (ethanol), 217 mμ (ε 24,800) and 269 (17,300); NMR (DMF-d_6) δ 2.05 ppm (3H, singlet, CH_3), 4.46 (2H, singlet, CH_2), 6.67 and 7.07 (1H and 2H respectively, broad, C_6H_3), 7.43 (5H, singlet, C_6H_5) and 10.70 (1H, broad, NH); mass spectrum (high resolution, major ions) (17) m/e 298 ($C_{16}H_{14}N_2O_2S$), 192 ($C_9H_8N_2OS$), 165 ($C_8H_9N_2S$), 150 (C_8H_6OS or $C_7H_6N_2S$), 149 ($C_7H_5N_2S$) and 105 (C_7H_5O).

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.62; H, 4.86; N, 9.31.

2-Benzamido-2′-hydroxy-4′-methylthioacetanilide (**9b**) by Hydrolysis of **7b**.

An amphorous, slightly yellow mixture of **7b** and **8b**, weighing 650 mg. (65%), was obtained from 1.00 g. of **5b** in the manner described above. To a stirred solution of the mixture in 80 ml. of tetrahydrofuran at room temperature, was added 6 ml. of 1.5 *N* of hydrochloric acid. After 10 minutes, the tetrahydrofuran was evaporated at 20°. To the residue was added 24 ml. of 1 *N* of potassium hydroxide followed by 60 ml. of water. Crude **8b** (TLC, m.p.) was collected as insoluble solid (310 mg., after washing with 0.1 *N* of sodium hydroxide). The alkaline filtrate and washings were combined and acidified with acetic acid. The precipitated mixture of **8b** and **9b** (TCL) weighed 295 mg. This solid mixture was stirred at room temperature with 20 ml. of 0.1 *N* of sodium hydroxide for 20 minutes. A second crop (107 mg.) of **8b** was collected as alkali insoluble material after washing with 0.1 *N* of sodium hydroxide. The combined filtrate and washings on acidification with acetic acid now gave pure **9b** (TLC, m.p.) weighing 156 mg.

The combined crops of **8b** were recrystallized twice from ethanol to give the pure material weighing 344 mg. (34%, based on starting *N*-oxide **5b**), as colorless flakes, m.p. 241-243° dec.

Phenol **9b** was recrystallized to constant m.p. from ethanol, yield 110 mg. (10%, based on starting *N*-oxide **5b**) of a light brown powder, m.p. 229-231°; IR (potassium bromide), 3350 and 3300 cm^{-1} (NH), 3400-2500 (broad, OH), 1660 and 1640 (CONH); mass spectrum (low resolution) m/e 316, 298, 193, 181, 166, 155, 140, 134, 126, 111 and 105.

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; H, 8.85; S, 10.13. Found: C, 60.71; H, 5.01; N, 8.82; S, 9.85.

2-Benzamido-2′-hydroxyacetanilide (**10**) (9a, 13).

A solution of 16 mg. (0.050 mmole) of **9b** in 8 ml. of ethanol was heated to a slow reflux on a steam bath. To the boiling solution was added 1 ml. of W-2 Raney nickel, which had been prewashed with methanol. Reflux was continued for 15 minutes with stirring. Upon partial cooling, the nickel was removed by filtration followed by washing with hot ethanol. The combined

filtrates were evaporated to dryness. The residual crude **10** (TLC) was purified by chromatography on a 20 cm x 20 cm plate of silica gel, 2 mm thick (developed in ether, main band eluted with 5% methanol in ethyl acetate). The purified **10**, after recrystallization from ethanol-water, weighed 2.0 mg. (15%) colorless prisms, m.p. 198-201°. This material was found to be identical with a synthetic sample (9a, 13) by mixture m.p. and comparison of IR spectra.

Acknowledgement.

We thank Dr. P. Bommer and his staff in our physical chemistry department, in particular, Dr. W. Benz for MS. Dr. F. Scheidl for elemental analyses, Dr. V. Toome for UV spectra, Mr. S. Traiman and Dr. H. Wyss for IR spectra, and Dr. T. Williams for NMR spectra.

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(14) The lamp was turned off every 5 minutes and the reaction mixture was analyzed by tlc. After 15 minutes, the starting material had disappeared and the solution contained essentially pure oxazirane **6b**.

(15) The Rf values on silica gel with ether were: **5b** = 0.04, **6b** = 0.46, **7** = 0.29 and **8b** = 0.32. Better separation of **7** and **8b** can be achieved by the use of ethyl acetate as eluent (Rf 0.61 and 0.70 respectively).

(16) During the laborious fractional recrystallizations most of compound **7** was lost. A better representation of the actual yield of both **7** and **8b** is given by the hydrolysis experiment (**7** to **9**).

(17) The elemental compositions reported here were determined on the basis of accurate mass measurements. The found values agreed with the calculated values to within 3 millimass units in all cases.

Received December 8, 1969 Nutley, New Jersey 07110