Quinazolines and 1,4-Benzodiazepines. XLVII.[1,2] A Novel Alcoholytic Ring Contraction of an Oxazirinobenzodiazepine

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7-Chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (1) undergoes a facile alcoholytic ring contraction to give 3-alkoxymethyl-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazolin-2(1H)-ones (**2a,b**) in good yields. The structures of **2a** and **2b** were established by chemical correlations as well as by direct synthesis. A mechanism for this conversion is discussed.

The study of the chemistry of oxazirinobenzodiazepines of type **1**[1] led to the finding that solutions of **1** in lower primary and secondary alcohols are unstable even at room temperature. The oxaziridine undergoes an unusual transformation which results in the addition of one molecule of the respective alcohol with concomitant ring contraction to 3-alkoxymethyl-3,4-dihydro-4-hydroxyquinazolin-2(1H)-ones of type **2**. In this paper, we wish to report the ethanolysis and the methanolysis of **1** which occur with 60–70% yield.

The physical and chemical properties indicated structures **2a** and **2b** for these alcoholysis products. The ir spectra showed the presence of NH and OH groups and amide carbonyls (1670 cm^{-1}). The nmr spectrum also showed the OH and NH protons; in addition the methylene groups attached to the 3-N appeared as AB quartets centering at about 4.7 ppm. The uv spectra were typical for systems of this type.[3]

On treatment with alcohols, the quaternary hydroxyl groups could be readily replaced by alkoxyl groups as shown by the conversion of **2a** to **7**. Hydrogenolysis of **2a** over a platinum catalyst yielded **8**. Both **2a** and **2b** were readily hydrolyzed by aqueous acids to the 6-chloro-4-phenyl-2(1H)-quinazolinone (**5**) which was identical with the quinazolinone prepared by the fusion of 2-amino-5-chlorobenzophenone (**9**) with urea.[4] Both **2a** and **5** gave the 2-*p*-toluenesulfonyloxyquinazoline **6** when treated with *p*-toluenesulfonyl chloride in pyridine. Reduction of **2a** with lithium aluminum hydride gave the tetrahydroquinazoline derivative **3** which was also obtained by reduction of **4**.[3] Finally we identified **2b** by an unequivocal synthesis from the aminochlorobenzophenone **9**. Reaction of **9** with methoxymethyl isocyanate[5] gave the expected[3] compound **2b**, which was found to be identical (mixture melting point and ir) with the methanolysis product of **1** (see Scheme I). The formation of compounds **2** from the oxaziridine **1** may be explained by a mechanism such as that shown in Scheme II. Thus, the oxazirinobenzodiazepine opens to form an imino isocyanate I which recyclizes readily by intramolecular attack of the basic imino nitrogen on the isocyanate function to give an intermediate II, which in turn is converted into **2** by the addition of alcohols. Formation of **2** from II is probably rapid since acylated imines are known[6–10] to add alcohols readily. This mechanism is supported by the observation that the 1-methyl analog of **1** (**10**) is stable in alcoholic solutions. It also suggests the possibility of base catalysis in these reactions. Indeed, catalytic amounts of hydroxide ions or even triethylamine reduce the reaction time from days to minutes. The presence of acid stops the reaction.

This mechanism also accommodates the observation that compound **1** is converted to **5** in aqueous tetrahydrofuran. Here, the formation of 3-hydroxymethylquinazoline is postulated as an intermediate which loses formaldehyde and water to yield **5**. Compound **5** appeared as a bluish fluorescent spot on silica gel chromatograms when viewed under uv light. The presence of **5** was detected in all chromatograms of crude product mixtures resulting from the alcoholyses of **1**, since the alcohols used were not rigidly dried.

Experimental Section[11]

7-Chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (1).—This oxaziridine, mp 136° dec, was obtained by photoisomerization of 7-chloro-1,3 dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide[12] as reported elsewhere.[1] Proof of structure along with some physical and chemical properties will appear elsewhere.[1]

6-Chloro-3,4-dihydro-3-ethoxymethyl-4-hydroxy-4-phenyl-2-(1H)-quinazolinone (2a).—A suspension of 25.0 g (87 mmol) of **1** in 4 l. of ethanol was stirred at room temperature for 8 days. In this period a clear solution formed and no starting material was detectable by tlc or starch–iodide test. The solvent was evaporated; recrystallization of the residual solid from acetonitrile gave 20.0 g (69%) of **2a** as colorless needles: mp 168.5–169.5°; ir (KBr) 3325, 3225, and 1670 cm^{-1}; uv max (*i*-PrOH) 251 mμ (ε 16,400), 295 (1850), and 304 (1600); molecular ion (low resolution) *m/e* 332 (calcd 332); δ (DMSO-d_6) 0.85 (3, t, CH_3), 3.23 (2, q, CH_2), 4.65 (2, ABq, NCH_2); 6.7–7.6 (8, m, aromatic), 7.20 (1, s, D_2O exchangeable, OH), and 10.00 ppm (1, s, D_2O exchangeable, NH).

Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; N, 8.42; Cl, 10.65. Found: C, 61.34; H, 5.20; N, 8.22; Cl, 10.87.

(1) Part XLVI: R. Y. Ning, G. F. Field, and L. H. Sternbach, *J. Heterocycl. Chem.*, in press.

(2) Presented in part at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970.

(3) W. Metlesics, G. Silverman, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **31**, 1007 (1966).

(4) T. S. Sulkowski and S. J. Childress, *ibid.*, **27**, 4424 (1962).

(5) This isocyanate was prepared by a modification of the procedure described by L. W. Jones and D. H. Powers [*J. Amer. Chem. Soc.*, **46**, 2518 (1924)].

(6) J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies, and T. H. Ramsay, *Aust. J. Sci. Res., Ser. A*, 330 (1948).

(7) W. Davies, T. H. Ramsay, and E. R. Stove, *J. Chem. Soc.*, 2633 (1949).

(8) Y. H. Suen, A. Horeau, and H. B. Kagan, *Bull. Soc. Chim. Fr.*, **5**, 1454, 1457 (1965).

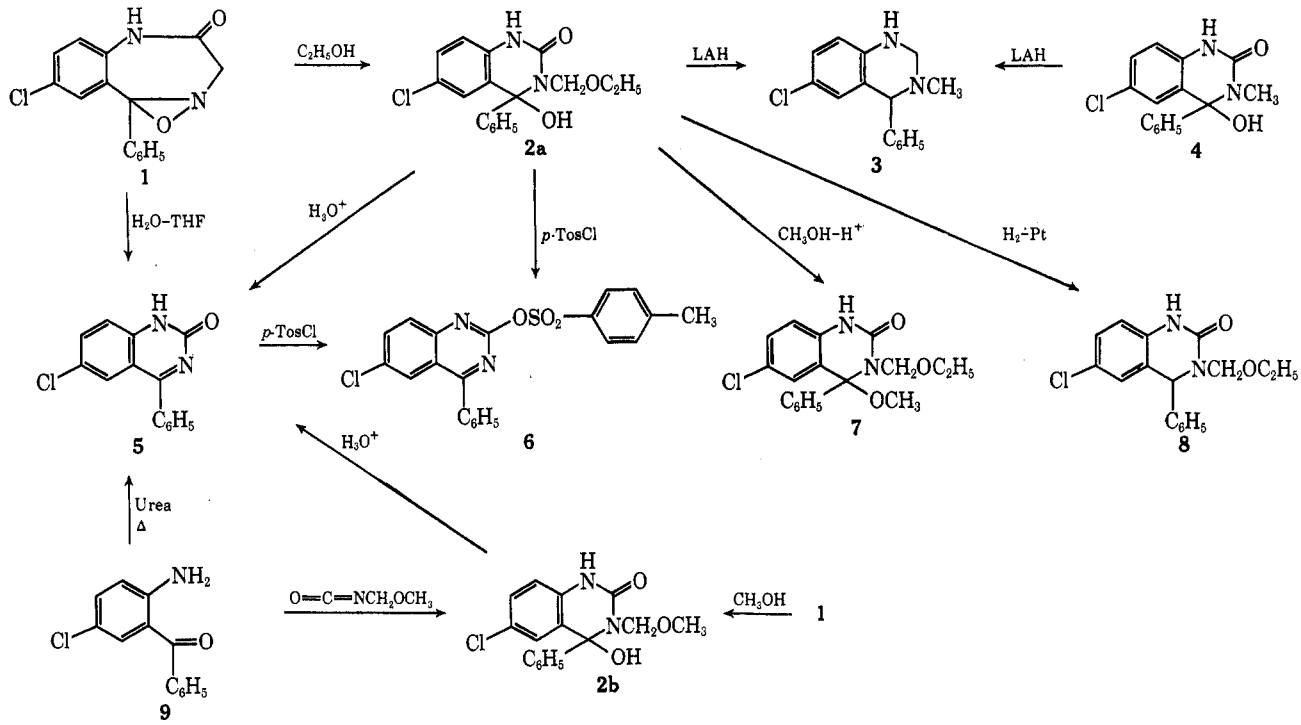
(9) S. W. Breuer, T. Bernath, and D. Ben-Ishai, *Tetrahedron*, **23**, 2869 (1967).

(10) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Org. Chem.*, **33**, 216 (1968).

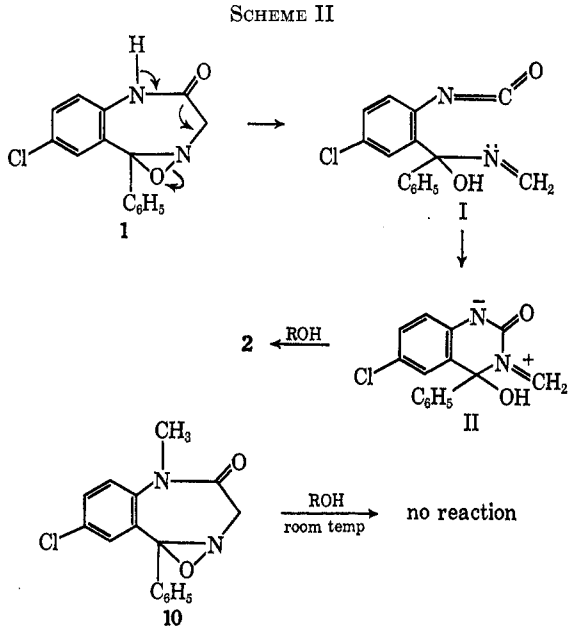
(11) All melting points were taken in a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were determined using a Beckman IR-9 or a Perkin-Elmer 621 grating spectrophotometer, mass spectra with a CEC-21-110 spectrometer, nmr spectra with a Varian A-60 spectrometer using tetramethylsilane as internal standard, and uv spectra with a Cary 14M or 15 recording spectrophotometer. All solvents used were of reagent grade purity. Ether refers to anhydrous diethyl ether. Unless otherwise specified, all solvents were evaporated with a Büchi Rotavapor evaporator, under water-aspirator pressure using a water bath set at 35–40°.

(12) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

SCHEME I



SCHEME II



Methoxymethyl Isocyanate.[5]—To a stirred suspension of 200 g (1.30 mol) of silver cyanate in 1 l. of anhydrous xylene was added, at room temperature, 81.0 g (1.00 mol) of freshly prepared and redistilled chloromethyl methyl ether.[13] The temperature rose from 23 to 49°. The reaction mixture was cooled to room temperature and stirred in an aluminum foil covered flask for 24 hr. The solids were removed by filtration and washed with xylene. The combined filtrate and washings were distilled and redistilled at atmospheric pressure through a Vigreux column. The fraction boiling between 89 and 94° (lit.[5] 89–90°) was collected: yield 53.5 g (61%); ir (film) 2280 cm^{-1}; δ (DMSO-d_6) 3.38 (CH_3), and 4.86 ppm (CH_2).

6-Chloro-3,4-dihydro-4-hydroxy-3-methoxymethyl-4-phenyl-2(1H)-quinazolinone (2b). A. From Oxaziridine 1.—A suspension of 17.5 g (61 mmol) of 1 in 2.6 l. of methanol was stirred at room temperature for 8 days. A clear solution was formed which did not contain any starting material 1. The methanol was evaporated and the residual solid recrystallized from acetonitrile to give 12.1 g (62%) of **2b**: colorless plates; mp 179.5–182.5°; ir (KBr) 3240 and 1670 cm^{-1}; uv max (*i*-PrOH) 251 mμ (ε 16,050), 295 (1900), and 304 (1600); molecular ion (low resolution) *m/e* 318 (calcd 318); δ (DMF-d_7) 3.10 (3, s, CH_3), 4.75 (2, AB q, CH_2), 6.8–7.6 (8, m, aromatic), 7.14 (1, s, D_2O exchangeable, OH), and 9.92 ppm (1, broad s, D_2O exchangeable, NH).

Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79; Cl, 11.12. Found: C, 60.47; H, 4.76; N, 8.49; Cl, 11.26.

Catalytic Effects of Acid and Bases on the Methanolysis of Oxaziridine (1). i. Control without Catalyst.—A suspension of 1.75 g (6.1 mmol) of oxaziridine 1 in 750 ml of methanol was stirred at room temperature. A clear solution formed overnight. The course of the reaction was monitored by tlc analyses (silica gel, ether) at intervals. After 38 hr, a small amount of 1 remained (tlc and starch–iodide test). Conversion to **2b** was complete in 2 days.

ii. With *p*-Toluenesulfonic Acid.—A suspension of 1.75 g (6.1 mmol) of 1 in 750 ml of methanol containing 10 mg of *p*-toluenesulfonic acid monohydrate was stirred at room temperature. A clear solution formed overnight. Tlc analysis of the solution at intervals showed that after 3 days no **2b** was detectable, and the bulk of 1 remained unchanged.

iii. With Benzyltrimethylammonium Hydroxide.—A suspension of 1.75 g (6.1 mmol) of 1 in 750 ml of methanol containing 1.0 ml of a 35% methanolic solution of benzyltrimethylammonium hydroxide was stirred at room temperature. A clear solution formed in 10 min. Tlc analysis showed that conversion to **2b** was complete within 15 min. After 1 hr, the methanolic solution was concentrated. Crystalline **2b** which precipitated was collected and washed thoroughly with methanol, yield 754 mg. A second crop of **2b** was obtained by concentration of the methanolic mother liquor and washings followed by dilution with water, yield 809 mg. The two crops were combined and recrystallized from acetonitrile to yield 1.40 g (72%) of **2b** as colorless platelets, mp 180–182°. A mixture melting point with authentic **2b** was undepressed.

iv. With Triethylamine.—A suspension of 1.75 g (6.1 mmol) of 1 in 500 ml of methanol containing 1.0 ml of triethylamine was stirred at room temperature for 20 min. The resulting clear solution was evaporated to dryness. The residual solid was recrystallized from acetonitrile to give 1.60 g (82%) of **2b** as colorless platelets, mp 183–184°. A mixture melting point with an authentic sample was undepressed.

B. Direct Synthesis.—A solution of 178 mg (0.77 mmol) of 2-amino-5-chlorobenzophenone and 65 mg (0.70 mmol) of methoxylmethyl isocyanate[6] in 5 ml of pyridine was allowed to stand at room temperature for 24 hr. The reaction mixture was

(13) A. H. Blatt, Ed., "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1941, p 377.

heated for 30 min on the steam bath and then poured onto ice. A yellow, partially solidified oil containing predominantly unreacted starting material which separated on standing was removed. The clear aqueous layer was diluted with more water until cloudy, then seeded with **2b**. On standing at 0°, **2b** crystallized. The yield, after washing with ether, was 53 mg (24%), mp 181–183°. A mixture melting point with **2b** obtained from methanolysis of **1** was undepressed; ir spectra and tlc in several solvent systems were identical.

6-Chloro-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (3). A. From 2a.—A solution of 1.0 g (3.0 mmol) of **2a** in 20 ml of dry tetrahydrofuran was added dropwise with stirring at room temperature over 30 min to a suspension of 1.14 g (30 mmol) of lithium aluminum hydride in 10 ml of tetrahydrofuran. The mixture was stirred at room temperature for 30 min, then heated to a gentle reflux for 2 hr. Excess hydride was decomposed with 2.4 ml of water and the solids were removed by filtration through a pad of Celite. Evaporation of the solvents gave 770 mg of an oil which partially crystallized on standing. This oily solid was triturated with hexane, chilled, and filtered to give 220.5 mg of crude **3**, mp 90–94°. The hexane filtrate was evaporated to dryness, and the oily residue, dissolved in benzene, was chromatographed on a short column of silica gel. After washing with 25% ether in benzene to remove fast moving impurities, 300 mg of relatively pure **3** was obtained by elution with ether. Combined crops of **3** after recrystallizations from hexane weighed 384 mg (50%): mp 95–96°; ir (KBr) 3200 cm^{-1}; δ (DMSO-d_6) 2.24 (3, s, CH_3), 3.46–3.88 (2, m, CH_2), and 4.49 ppm (1, s, CH).

Anal. Calcd for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.84; N, 10.83; Cl, 13.70. Found: C, 69.52; H, 6.06; N, 10.76; Cl, 13.21.

B. From 6-Chloro-3,4-dihydro-4-hydroxy-3-methyl-4-phenyl-2(1H)-quinazolinone (4).—To a suspension of 2.70 g (70 mmol) of lithium aluminum hydride in 80 ml of dry tetrahydrofuran was added batchwise with stirring at room temperature, 2.00 g (70 mmol) of **4**.[3] A mildly exothermic reaction occurred. Stirring at room temperature was continued for 30 min. After refluxing for 2 hr, the reaction mixture was decomposed with 5.4 ml of water, stirred vigorously for 10 min, and then filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was crystallized from hexane to give 1.25 g of **3**, mp 90–93°. After recrystallization from hexane, the yield was 1.04 g (57%), mp 92–95°. This material was identical with **3** obtained from **2a** by tlc and ir spectrum.

6-Chloro-4-phenyl-2(1H)-quinazolinone (5).[4] **A. From 1.**—A solution of 1.00 g (3.5 mmol) of **1** in a mixture of 25 ml of tetrahydrofuran and 12 ml of water was allowed to stand at room temperature. After 7 days, the solid that precipitated weighed 964 mg, mp 309–312°, and was found by tlc to be predominantly **5**. After recrystallizations from large volumes of acetonitrile, there was obtained 387 mg (43%) of pure **5**, mp 311–313°, identical with the authentic sample[4] by mixture melting point, ir, and tlc.

B. From 2b.—To a mixture of 25 ml of water and 35 ml of 6 *N* hydrochloric acid was added 1.00 g (3.0 mmol) of **2b**. The suspension was kept in a sealed flask inside an oven at 85–95° for 1 day. Water was evaporated. The residual solid was stirred with aqueous sodium bicarbonate, filtered, and washed with water. The dried solid was pure **5** by tlc: mp 311–314°; yield 777 mg (100%). A mixture melting point with an authentic sample was undepressed.

C. From 2a.—A solution of 1.0 g (3.0 mmol) of **2a** and 570 mg of *p*-toluenesulfonic acid monohydrate in 750 ml of methylene chloride was allowed to stand for 20 hr. The mixture was evaporated to dryness. The residual solid was washed with aqueous sodium bicarbonate then with water. The crude **5** obtained was recrystallized from acetonitrile: yield 692 mg (90%), mp 311–313.5°. A mixture melting point with an authentic sample was undepressed.

6-Chloro-4-phenyl-2-*p*-toluenesulfonyloxyquinazoline (6). A. From 2a.—A solution of 250 mg (0.75 mmol) of **2a** and 429 mg (2.25 mmol) of *p*-toluenesulfonyl chloride in 2 ml of pyridine was allowed to stand overnight at room temperature. The reaction mixture was poured into water. The oil that separated crystallized on standing, weight 211 mg. The solid was dissolved in methylene chloride and on standing, 9.6 mg of 6-chloro-4-phenyl-2(1H)-quinazolinone (**5**) crystallized, mp 303–310°. After recrystallization from acetonitrile, the yield was 4.0 mg (2.1%), mp 309–311°, mixture melting point with **5** undepressed.

The methylene chloride mother liquor was passed through a bed of silica gel. Elution with ether gave 194 mg of an oil which crystallized on standing. Recrystallizations from benzene–hexane mixtures gave 114 mg (37%) of **6**; mp 122–123.5°; ir (KBr) no NH band, 1600–1700 cm^{-1} clear; uv max (*i*-PrOH) 233 mμ (ϵ 53,500), 269 (10,000), and 336 (6700).

Anal. Calcd for $C_{21}H_{15}ClN_2O_3S$: C, 61.39; H, 3.67; N, 6.81; Cl, 8.62; S, 7.80. Found: C, 61.38; H, 3.74; N, 6.91; Cl, 8.84; S, 7.86.

B. From 5.—A solution of 192.5 mg (0.75 mmol) of **5** and 858 mg (4.50 mmol) of *p*-toluenesulfonyl chloride in 33 ml of dry pyridine was allowed to stand at room temperature for 4 days. The reaction mixture was poured onto ice. The tosylate **6** crystallized as flakes, yield 73.7 mg, mp 118–121°. After recrystallizations from benzene–hexane mixtures, the yield was 44 mg (14%), mp 122–124°; a mixture melting point with the tosylate obtained from **2a** above was undepressed.

6-Chloro-3,4-dihydro-3-ethoxymethyl-4-methoxy-4-phenyl-2(1H)-quinazolinone (7).—A solution of 7.0 g (20 mmol) of **2a** and 58 mg of *p*-toluenesulfonic acid monohydrate in 350 ml of methanol was stirred at room temperature for 2 hr. The reaction mixture was passed through a bed of Florisil which was then washed with some methanol. The filtrate was evaporated to dryness. The residue was dissolved in methylene chloride and filtered through a fresh bed of Florisil, which was then eluted with ether. The combined effluent was evaporated to dryness. The residual oil, crystallized from ether and hexane and then recrystallized from acetonitrile, gave 5.55 g (76%) of **7** as prisms: mp 172–173°; ir (KBr) 3200 and 1680 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.33; H, 5.52; N, 8.08; Cl, 10.22. Found: C, 62.42; H, 5.55; N, 8.09; Cl, 10.13.

6-Chloro-3,4-dihydro-3-ethoxymethyl-4-phenyl-2(1H)-quinazolinone (8).—A solution of 10.0 g (30 mmol) of **2a** in 250 ml of tetrahydrofuran was hydrogenated (1 atm) in the presence of 2.50 g of platinum oxide until the rate of hydrogen uptake became very slow. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residual gum crystallized from ethanol to give 3.30 g (35%) of **8** as plates: mp 172–174°; ir (KBr) 3200 and 1680 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84; Cl, 11.19. Found: C, 64.28; H, 5.44; N, 8.64; Cl, 10.79.

7-Chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (10).—A solution of 30 g (0.10 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide[12] in 1.4 l. of tetrahydrofuran was irradiated with a Hanovia 250 W medium-pressure mercury lamp (No. 654 A) through a Pyrex filter under nitrogen at 20° for 22 hr. The solution was evaporated to dryness and the residual gum was crystallized from ethanol. One recrystallization from ethanol gave 22.1 g (74%) of **10** as colorless prisms: mp 99–100°; ir (KBr) 1690 cm^{-1}; uv max (*i*-PrOH) 252 mμ (ϵ 11,300).[14]

Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31; Cl, 11.78. Found: C, 63.71; H, 4.42; N, 9.36; Cl, 11.92.

Compound **10** also gave the positive starch–iodide test typical of oxaziridines.[15]

Attempted Alcoholyses of Oxaziridine 10.—A solution of 1.13 g (4.0 mmol) of **10** in 100 ml of methanol was allowed to stand for 2 weeks at room temperature. The reaction mixture gave a strongly positive starch–iodide test and tlc indicated negligible reaction. Repetition of the experiment using ethanol gave the same results.

Registry No.—**2a**, 24605-69-4; **2b**, 24621-38-3; **3**, 24621-39-4; **6**, 24621-40-7; **7**, 24621-41-8; **8**, 24621-42-9; **10**, 24605-70-7.

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(14) The absence of a nitrone chromophore is evident from comparison with the uv spectrum of the starting material: uv max (*i*-PrOH) 239 mμ (ϵ 31,000), 266 (inflection, 15,000), and 310 (11,500).

(15) For a recent review, see J. F. Dupin, *Bull. Soc. Chim. Fr.*, 3085 (1967).