of 5.0×10^{-3} M. The following absorption maxima (nm) were observed: for water, 292 (ε 24); for aqueous NaLS, 290 (ε 37); for aqueous dioxane, 306 (ε 55); and for heptane, 330 (ε 258).

Spectra were obtained for 2.0×10^{-4} M solutions of bromine in water, aqueous NaLS, and heptane. The concentration of NaLS was 1.95×10^{-2} M, which corresponds to a micelle concentration of 2.0×10^{-4} M. The following absorption maxima (nm) were observed: for water, 260 (shoulder, ε 83) and 392 (ε 82); for aqueous NaLS, 260 (shoulder, ε 66) and 392 (ε 76); and for heptane, 417 (ε 157).

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Registry No.—NaLS, 151-21-3; NaL, 629-25-4; CTABr, 57-09-0; lauric acid, 143-07-7; methyl laurate, 111-82-0; lauryl alcohol, 112-53-8; laurylsulfuric acid, 151-41-7.

References and Notes

(1) For reviews, see (a) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., 1975; (b) C. A. Bunton, *Prog. Solid State Chem.*, **8**, 239 (1973); (c) E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, **8**, 271 (1970).

(2) F. M. Menger, J. U. Rhee, and H. K. Rhee, *J. Org. Chem.*, **40**, 3803 (1975).

(3) For examples, see (a) C. N. Sukenik, B.-A. Weissman, and R. G. Bergman, *J. Am. Chem. Soc.*, **97**, 445 (1975); (b) R. A. Moss, C. J. Talkowski, D. W. Reger, and C. E. Powell, *ibid.*, **95**, 5215 (1973); (c) R. A. Moss and W. L. Sunshine, *J. Org. Chem.*, **39**, 1083 (1974); (d) J. M. Brown and C. A. Bunton, *J. Chem. Soc., Chem. Commun.*, 969 (1974); (e) D. Hindman and J. Jacobus, *Tetrahedron Lett.*, 1619 (1974), and references cited therein.

(4) J. V. Braun, H. Deutsch, and A. Schmatloch, *Ber.*, **45**, 1246 (1912).

(5) In a related study Breslow and co-workers[6] have examined the influence of cyclodextrins on the regioselectivity of anisole monochlorination in aqueous hypochlorous acid.

(6) R. Breslow and P. Campbell, *J. Am. Chem. Soc.*, **91**, 3085 (1969); (b) R. Breslow and P. Campbell, *Bioorg. Chem.*, **1**, 140 (1971); (c) R. Breslow, H. Kohn, and B. Siegel, *Tetrahedron Lett.*, 1645 (1976).

(7) A comparison with different substrates is being made, but it can be reasonably assumed that in aqueous hypochlorous acid **1** would give a para/ortho ratio very close to that reported for anisole. Monochlorination of **1**, *n*-nonyl phenyl ether, and *n*-dodecyl phenyl ether in 40:60 (v/v) water–dioxane with hypochlorous acid gave para/ortho ratios of 3.2, 3.3, and 3.6, respectively.[8] These results indicate that in a homogeneous nonmicellar medium the para/ortho ratio is influenced only slightly by chain length.

(8) D. A. Jaeger and R. E. Robertson, unpublished results.

(9) For example, the micelle surface pH should increase on going from NaLS to NaL to CTABr.

(10) (a) P. Mukerjee and K. J. Mysels, *Natl. Stand. Ref. Data Serv., Natl. Bur. Stand.*, **No. 36**, 66 (1971); (b) *ibid.*, **No. 36**, 107 (1971).

(11) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. 3, Academic Press, New York, N.Y., 1972, pp 114–123.

(12) A. N. Campbell and G. R. Lakshminarayanan, *Can. J. Chem.*, **43**, 1729 (1965).

(13) R. C. Merrill and R. Getty, *J. Phys. Chem.*, **52**, 774 (1948).

(14) R. A. Smith, *J. Am. Chem. Soc.*, **55**, 3718 (1933).

(15) G. Brauer, "Handbook of Preparative Inorganic Chemistry", 2nd ed, Vol. 1, Academic Press, New York, N.Y., 1963, p 308.

(16) D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry", 2nd ed, Holt, Rinehart, and Winston, New York, N.Y., 1969.

(17) A short-wavelength absorption maximum at 220 nm is reported here, but analogous maxima are not for those spectra above and for most of those below due to instrumental limitations (Beckman DB) in the short-wavelength region.

Quinazolines and 1,4-Benzodiazepines. 80.[1] 1-Hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, a Hydroxamic Acid via an Amidine *N*-Oxide

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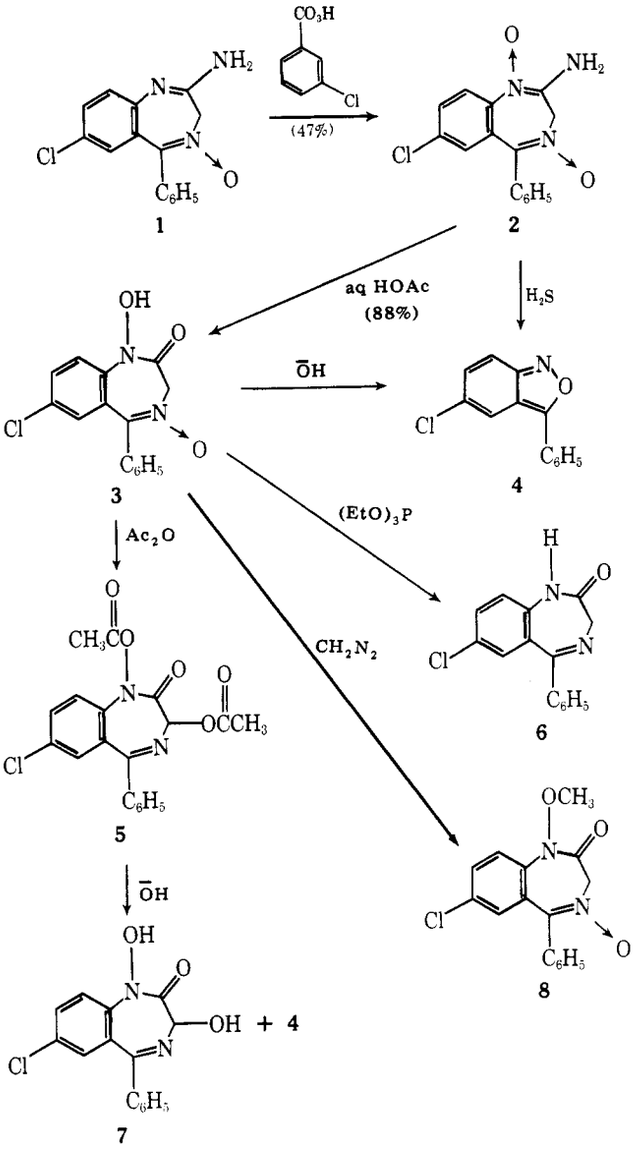
We wish to record the preparation of a novel class of 1,4-benzodiazepines which contain oxygenated nitrogen atoms in position 1. Also of interest was the preparation of the amidine *N*-oxide[2] **2** by peracid oxidation of amidine **1**[3] and the efficient hydrolysis of compound **2** to the hydroxamic acid **3**.

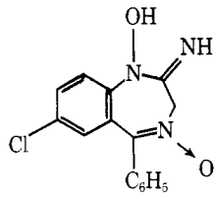
When a solution of 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**1**)[4] in methylene chloride was treated with a slight excess of *m*-chloroperbenzoic acid at room temperature, oxidation was complete in minutes and the amidine *N*-oxide **2** was readily isolated, as yellow prisms, in 47% yield (Scheme I). Compound **2** was soluble in both dilute aqueous acids and bases, and was very susceptible to hydrolysis. For example, if a solution of **2** in aqueous acetic acid was allowed to stand at room temperature, the insoluble hydroxamic acid **3** precipitated and was obtained in 88% yield. Mild treatment of **2** with anhydrous hydrogen sulfide afforded a complex mixture from which only 5-chloro-3-phenyl-2,1-benzisoxazole[5] (**4**) was isolated (49%). The same degradation product **4** was obtained (87% yield) when the hydroxamic acid **3** was dissolved in 1 N sodium hydroxide at room temperature. An attempt to deoxygenate the 4-oxide function of **3** with triethyl phosphite resulted in a simultaneous reduction of the hydroxamic acid to the lactam–imine, compound **6**,[6] which was isolated in 24% yield. The acidic character of the hydroxamic acid was evident by the smooth O-methylation of **3** with diazomethane to give **8**. When **3** was heated in acetic anhydride, the 1,3-diacetoxy derivative **5** was obtained. Mild alkaline hydrolysis of **5** afforded a mixture of the 1,3-dihydroxy compound **7** and the 2,1-benzisoxaole **4**, which again indicated the destabilizing influence of the 1-hydroxy substituent on the benzodiazepine ring toward cleavage by nucleophiles.

A comparison of the NMR and UV spectra of **2** and **3** indicated that none of the hydroxyamidine tautomer **9** exists in

Scheme I



solution. Compound 3 served as a model for the tautomeric structure 9. The hydroxyl proton of 3 appeared at δ 11.07 in



9

the NMR spectrum, while the spectrum of 2 showed an NH_2 signal at δ 7.9–8.4; the methylene protons in position 3 of 3 were nonequivalent, appearing as a broad AB quartet, while the methylene group in both 1 and 2 appeared as singlets. Furthermore, the UV spectrum of 2 was quite different than that of 3.

Experimental Section[7]

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 1,4-Dioxide (2). To a stirred suspension of 6.80 g (24.0 mmol) of 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (1)[4] in 70 mL of methylene chloride, chilled in an ice bath, was added in portions 5.90 g (28.8 mmol) of *m*-chloroperbenzoic acid (technical grade, 85%). The ice bath was removed and stirring was continued for 0.5 h. A brown solution was formed and a starch–iodide test indicated little or no remaining peracid. Triethylamine (5 mL, 35 mmol) was added and the precipitated solids were collected to give 3.4 g (47%) of 2, mp 211 °C dec. Recrystallization from ethanol afforded yellow prisms: mp 221 °C; IR (KBr) 3400–3060 (br) and 1548 cm^{-1}; NMR (Me_2SO-d_6) δ 4.78 (s, 2, CH_2), 6.90 (d, 1, H-6), 7.47 (m, 5, C_6H_5), 7.57 (q, 1, H-8), 8.14 (d, 1, H-9), and 7.9–8.4 (br, 2, NH_2); UV max (2-PrOH) 220 nm (sh, ε 19 000), 244 (18 750), 288 (26 700), and 370 (sh, 1310); mass spectrum *m/e* 301 (M^+).

Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.92. Found: C, 59.79; H, 4.38; N, 14.10.

Diacetic Acid Salt of 2. A solution of 4.0 g (13.3 mmol) of 2 in 15 mL of glacial acetic acid was diluted with 70 mL of ether. Colorless prisms which crystallized were collected. The weight was 4.9 g (88%), mp 145–148 °C dec, UV spectrum identical with that of 2.

Anal. Calcd for $C_{15}H_{12}ClN_3O_2 \cdot 2C_2H_4O_2$: C, 54.10; H, 4.78; N, 9.96. Found: C, 54.22; H, 4.91; N, 9.89.

7-Chloro-1,3-dihydro-1-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (3). A solution of 8.0 g (26.6 mmol) of 2 in 100 mL of 50% aqueous acetic acid was diluted with 200 mL of water and left at room temperature overnight. The solids which precipitated were collected, in two crops, to give 7.0 g (88%) of the desired product, mp 212–213 °C dec. Recrystallization from ethyl acetate afforded yellow prisms: mp 219–220 °C dec; IR (KBr) 2950–2370 (salt bands) and 1700 cm^{-1} (carbonyl); UV max (2-PrOH) 243 nm (ε 26 800) and 311 (9620); NMR (Me_2SO-d_6) δ 4.50 and 4.80 (br s, 1 each, CH_2), 6.97 (d, 1, 6-H), 7.4–7.8 (m, 7, arom) and 11.07 (s, 1, OH); mass spectrum *m/e* 302 (M^+).

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.55; H, 3.68; N, 9.15.

5-Chloro-3-phenyl-2,1-benzisoxazole (4).[5] (a) From 2. Into a stirred suspension of 151 mg (0.5 mmol) of 2 in 5 mL of tetrahydrofuran at room temperature was introduced a stream of hydrogen sulfide gas for 15 min. The reaction mixture was separated by preparative thin-layer chromatography on silica gel. The main band (R_f 0.75 in 10% ether–benzene) was collected by elution with 10% methanol–ethyl acetate. Crystallization from methanol of the residue, after removal of solvents, gave 50 mg (49%) of yellow needles, mp 113–114 °C. This material was identical with a known sample of 4[5] by TLC, IR, and mixture melting point.

(b) From 3. A solution of 0.3 g (1.0 mmol) of 3 in 10 mL of 1 N aqueous sodium hydroxide was left at room temperature overnight. Yellow needles that formed were collected and washed with water. The yield was 200 mg (87%), mp 111–113 °C. This material was identified by TLC, IR, and mixture melting point as 4.

In a separate experiment, a solution of 3 in tetrahydrofuran was saturated with concentrated hydrochloric acid and left at room temperature overnight. The 2,1-benzisoxazole 4 again was isolated in high yield.

7-Chloro-1,3-diacetoxy-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (5). A suspension of 3.0 g (10 mmol) of 3 in 8 mL of acetic anhydride was heated gently on a steam bath for 2 h; a clear solution formed after 5 min. On cooling, 5, which crystallized as prisms, was collected and washed with benzene followed by hexane. It weighed 3.1 g (80%), mp 197–199 °C. Recrystallization from tetrahydrofuran–petroleum ether afforded colorless prisms; mp 196–198 °C; IR (KBr) 1810, 1755, and 1725 cm^{-1}; NMR (DMF-d_7) δ 2.29 (s, 3, 3-$OCOCH_3$), 2.39 (s, 3, 1-$OCOCH_3$), 6.17 (s, 1, CHOAc), and 7.5–8.0 (m, 8, arom); UV max (CH_3CN) 231 nm (ε 31 000), 253 (sh, 16 700), and 309 (sh, 2120); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{19}H_{15}ClN_2O_5$: C, 59.00; H, 3.91; N, 7.24; Cl, 9.17. Found: C, 59.18; H, 3.87; N, 7.38; Cl, 9.04.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6).[6] Reduction of 3 with Triethyl Phosphite. A suspension of 0.3 g (1.0 mmol) of 3 in 2 mL of triethyl phosphite was heated on a steam bath for 2.5 h. A clear solution gradually formed. The reaction mixture was separated by preparative thin-layer chromatography on silica gel. The main band (R_f 0.71 in ethyl acetate) was collected, eluted with 10% methanol in ethyl acetate, and evaporated. Crystallization of the residue from ethyl acetate–ether gave 65 mg (24%) of 6 as colorless prisms, mp 209–211 °C. This material was identified as 6[6] by TLC, IR, and mixture melting point.

7-Chloro-1,3-dihydro-1,3-dihydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7). To a solution of 0.77 g (2.0 mmol) of 5 in 10 mL of tetrahydrofuran at room temperature was added 6 mL of 1 N aqueous sodium hydroxide. The two-phase mixture was stirred vigorously overnight. Tetrahydrofuran was evaporated. The aqueous layer was further basified to pH 11 with 0.1 N aqueous sodium hydroxide and extracted with methylene chloride. The organic layer was separated, dried, and evaporated. Crystallization of the residue from methanol gave 90 mg (20%) of 5-chloro-3-phenyl-2,1-benzisoxazole (4) as yellow needles, mp 109–111 °C. This material was identified as 4 by TLC, IR, and mixture melting point.

The aqueous layer was acidified with acetic acid and extracted with methylene chloride. The organic layer was separated, dried, and evaporated. Crystallization of the residue from ether gave 140 mg of crude 7, which on recrystallization from ethanol–water gave 75 mg (23%) of cream prisms; mp 176–178 °C dec; IR (KBr) 3240–3110 (br) and 1687 cm^{-1}; UV max (2-PrOH) 233 nm (ε 28 200), 260 (sh, 16 900), and 324 (2240); NMR (Me_2SO-d_6) δ 4.69 (d, J = 9 Hz, 1, 3-OH), 6.34 (d, J = 9 Hz, 1, CH), 7.15 (m, 1, 6-H), 7.41 (m, 5, C_6H_5), 7.61 (m, 2, 8-H and 9-H), and 10.77 (s, 1, NOH); mass spectrum *m/e* 302 (M^+).

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.38; H, 3.80; N, 9.27.

7-Chloro-1,3-dihydro-1-methoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (8). To a stirred solution of 6.2 g (22 mmol) of 3 in 250 mL of tetrahydrofuran at room temperature was added, in portions, an ethereal solution of diazomethane until gas evolution ceased. A few drops of acetic acid were added to decompose excess diazomethane. Solvents were evaporated. Crystallization of the residue from ethyl acetate gave 2.7 g of crude 8. Recrystallization from ethyl acetate afforded 1.8 g (34%) of colorless prisms: mp 195–197 °C; IR (KBr) 1718 and 1240 cm^{-1}; NMR ($CDCl_3$) δ 3.81 (s, 3, OCH_3); mass spectrum *m/e* 316 (M^+).

Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.61; H, 4.27; N, 9.09.

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Registry No.—1, 7722-15-8; 2, 63076-85-7; 2 diacetic acid salt, 63076-86-8; 3, 63076-87-9; 4, 719-64-2; 5, 63076-88-0; 6, 1088-11-5; 7, 63076-89-1; 8, 63076-90-4.

References and Notes

(1) Part 79: N. W. Gilman and R. I. Fryer, *J. Heterocycl. Chem.*, in press.
(2) Amidine *N*-oxides, sometimes assigned the tautomeric structures of *N*-hydroxyamidines, have appeared sporadically in the literature: (a) E. Bamberger and F. Tschirner, *Ber.*, **35**, 714 (1902); (b) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924); (c) H. G. Aurich, *Chem. Ber.*, **101**, 1761 (1968); (d) L. H. Briggs, R. C. Cambie, I. C. Dean, and P. S. Rutledge, *Aust. J. Chem.*, **29**, 357 (1976).
(3) Such an oxidative process appeared recently in the patent literature: Y. Kuwada, H. Natsugari, and K. Meguro; U.S. Patent 3 900 490 (1975).
(4) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).
(5) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).
(6) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).
(7) General comments on experimental details may be found in a previous paper: R. Y. Ning, R. I. Fryer, P. B. Madan, and B. C. Sluboski, *J. Org. Chem.*, **41**, 2720 (1976).