Quinazolines and 1,4-Benzodiazepines. LXV (1) Some Transformations of Chlordiazepoxide

Armin Walser, R. Ian Fryer, and Leo H. Sternbach*

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

and

Michael C. Archer

Massachusetts Institute of Technology, Department of Nutrition and Food Science
Cambridge, Massachusetts 02134

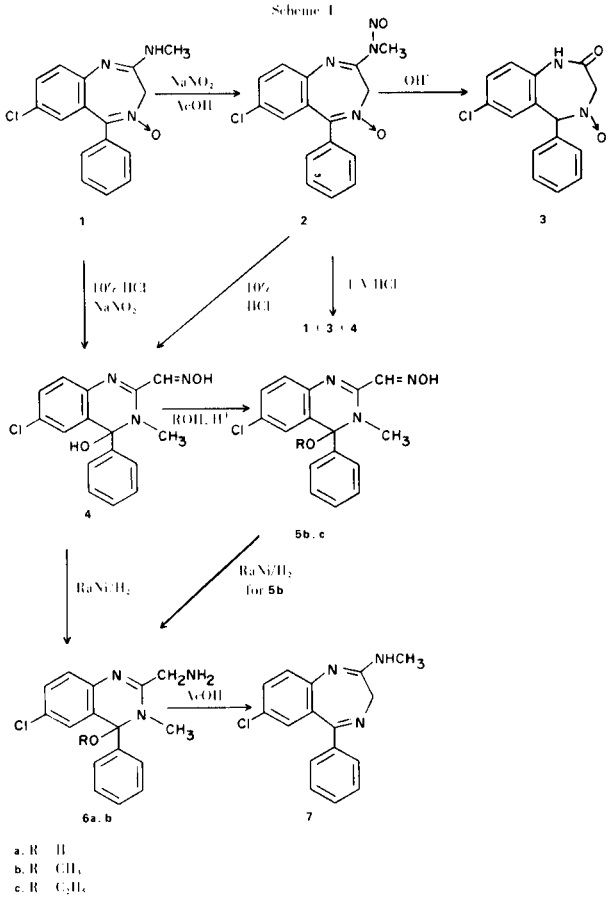
Received February 6, 1974

Our interest in the chemistry of chlordiazepoxide **1** and related compounds (2) prompted us to investigate the products obtained by treatment of this compound with nitrous acid. Depending on the reaction conditions used, two products could be readily obtained. In an acetic acid medium, the nitrosoamidine **2** (Scheme I) was formed, whereas in hydrochloric acid an excellent yield of the dihydroquinazoline derivative **4** was isolated.

Compound **2** was readily cleaved on treatment with alkali or acid. Treatment with 1 *N* aqueous sodium hydroxide at room temperature resulted in a nearly quantitative conversion into the lactam **3** (3) with liberation of diazomethane (4). Hydrochloric acid (1 *N*) cleaved the nitrosoamidine **2** within 15 minutes to a mixture of chlordiazepoxide **1**, the lactam **3**, and the quinazoline **4**. This quinazoline was formed as the main product when the nitrosoamidine **2** was treated with 10% hydrochloric acid and was obtained as mentioned above in high yield by the nitrosation of **1** in hydrochloric acid.

The structure of the quinazoline **4**, based on analytical and spectroscopic data was also substantiated by the chemical transformations described below. Recrystallization of the hydrochloride of **4** from solvent mixtures containing methanol resulted in partial conversion to **5b**. This methoxy derivative as well as the corresponding ethoxy compound **5c** were formed in good yield when the hydrochloride of **4** was refluxed for 1 to 2 hours in the corresponding alcohol. Catalytic reduction of the oximes **4** and **5b** with Raney nickel led to the aminomethylquinazolines **6a, b**. As expected, these rather labile aminomethylquinazolines were transformed into the 4-desoxy derivative of chlordiazepoxide, compound **7** (3), by heating under reflux in acetic acid for a short period of time.

Scheme I



The unusual formation of the quinazoline **4** during nitrosation of chlordiazepoxide can be explained as follows. Hydrolytic cleavage of the nitrone and alternate recyclization would lead to the intermediate 6-chloro-3,4-dihydro-4-hydroxy-2-hydroxyaminomethyl-3-methyl-4-phenyl-

quinazoline in a reversible reaction. The oxidation of this hydroxylamine to the oxime **4** by nitrous acid may be the result of nitrosation of the hydroxylamine and elimination of nitroxyl (5).

EXPERIMENTAL (6)

7-Chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (**2**).

Over a period of 30 minutes, 18 g. (0.26 mole) of sodium nitrite was added in small portions to a stirred solution of 60 g. (0.2 mole) of **1** (2) in 400 ml. of glacial acetic acid. After the addition was completed, the mixture was stirred for another 30 minutes at room temperature.

The product was precipitated in crystalline form by gradually adding 400 ml. of water. The precipitate was collected, washed with water and dissolved in 500 ml. of methylene chloride. The solution was washed with saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated. After addition of 200 ml. of 2-propanol, the rest of the methylene chloride was evaporated under reduced pressure.

The crystals were collected, washed with 2-propanol and dried to leave 49 g. (75%) of **2** as light yellow prisms, m.p. 158-160° dec. The analytical sample was recrystallized from ether/hexane, m.p. 158-160° dec.; uv (2-propanol) λ max 239 mμ (ε, 28,000), 294 (ε, 27,000), 397/8 (390), 415 (280); nmr (deuteriochloroform): δ 3.43 ppm (s, 3, NCH_3), 5.4 (broad s, 2, $-CH_2-$), 7-8 (m, 8, aromatic proton).

Anal. Calcd. for $C_{16}H_{13}ClN_4O_2$: C, 58.4; H, 4.0; N, 17.0. Found: C, 58.1; H, 3.8; N, 17.0.

6-Chloro-3,4-dihydro-4-hydroxy-3-methyl-4-phenylquinazoline-2-carboxaldoxime (**4**).

A. From Compound **1**.

A solution of 30 g. (0.1 mole) of **1** in 750 ml. of 3*N* (7) hydrochloric acid was treated with 10 g. (0.145 mole) of sodium nitrite. After stirring for 15 minutes at room temperature, the precipitated material was collected, washed with water and recrystallized from a mixture of 2-propanol and water to yield 25 g. (71%) of the hydrochloride of **4** as light yellow crystals, m.p. 182-185° dec.; uv (2-propanol) λ max 241 mμ (ε, 17,600) 316 (ε, 8,500); nmr (DMSO): δ 3.12 ppm (s, 3, $N-CH_3$), 6.94 (d, 1, J = 2 Hz, C_5-H), 7.3-7.9 (m, 7, aromatic H), 8.43 (s, 1, -CH=N), 8.81 (broad s, 1, OH), 13.55 (broad s, 1, OH).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_2 \cdot HCl$: C, 54.6; H, 4.3; N, 11.9; Cl^-, 10.1. Found: C, 54.5; H, 4.6; N, 11.7; Cl^-, 9.9.

For conversion to the free base, 5 g. of the above hydrochloride was dissolved by heating in 200 ml. of water and 100 ml. of 2-propanol. Concentrated ammonia (4.0 ml.) was added and the solution was cooled. The crystals which were separated were collected, washed with water, 2-propanol and ether to leave 4 g. (89%) of **4** as light yellow prisms, m.p. 193-195° dec.; uv (2-propanol) λ max 237 mμ (ε, 19,500) infl 317 (ε, 9,800) 330 (ε, 10,400); nmr (DMSO): δ 2.95 ppm (s, 3, $N-CH_3$), 6.85 (d, 1, J = 2 Hz, C_5-H), 7-7.8 (m, 8, aromatic H and OH), 7.94 (s, 1, CH=N), 11.8 (s, 1, OH).

B. From Compound **2**.

A suspension of 3.3 g. (0.01 mole) of **2** in 100 ml. of 3*N* hydrochloric acid was stirred at room temperature for 4 hours. The precipitate was collected, partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The insoluble material was collected, washed with water, 2-propanol and ether to leave 3 g. (95%) of almost pure **4**, m.p. and mixed m.p. with a sample obtained in **A** above 180-185° dec.

6-Chloro-3,4-dihydro-3-methyl-4-methoxy-4-phenylquinazoline-2-carboxaldoxime (**5b**).

A solution of 35.3 g. (0.1 mole) of the hydrochloride of **4** in 1 l. of methanol was heated under reflux for 2 hours with distillation of 200 ml. of methanol. The remaining solution was made alkaline by the addition of concentrated ammonia and the product was crystallized by dilution with water and cooling to 0°. The crystals were collected, washed with water and recrystallized from methanol to give 16.3 g. (49%) of **5b** as colorless prisms, m.p. 192-195° dec.; uv (2-propanol) λ max 239 mμ (ε, 20,100) sh 317/8 (ε, 10,800) 329 (ε, 11,200); nmr (DMSO): δ 2.87 ppm (s, 3, $O-CH_3$), 2.98 (s, 3, NCH_3), 6.75 (d, 1, J = 2 Hz, C_5-H), 7-7.7 (m, 7, aromatic H), 8.0 (s, 1, CH=N), 11.9 (s, 1, =NOH).

Anal. Calcd. for $C_{17}H_{16}ClN_3O_2$: C, 61.9; H, 4.9; N, 12.7. Found: C, 61.7; H, 4.7; N, 12.5.

6-Chloro-3,4-dihydro-4-ethoxy-3-methyl-4-phenylquinazoline-2-carboxaldoxime (**5c**).

A solution of 7 g. (0.02 mole) of the hydrochloride of **4** was heated under reflux in 200 ml. of ethanol for 1 hour with distillation of 100 ml. of ethanol. The remaining solution was made alkaline by the addition of concentrated ammonia. The crystals which precipitated upon the addition of water were collected, washed with water, ethanol and ether to leave 4.8 g. (70%) of product, m.p. 195-198° dec. Recrystallization from a mixture of ethanol and tetrahydrofuran afforded the analytical sample, m.p. 202-204° dec.; uv (2-propanol) λ max 238 mμ (ε, 18,400) sh 315 (ε, 10,600) 329 (ε, 11,000); nmr (DMSO): δ 1.18 (t, 3, J = 7 Hz, CH_3), 2.95 (s, 3, $N-CH_3$), 3.11 (m, 2, OCH_2), 6.90 (d, 1, J = 2 Hz, C_5-H), 7-7.77 (m, 7, aromatic H), 8.05 (s, 1, CH=N), 11.85 (s, 1, =NOH).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_2$: C, 62.9; H, 5.3; N, 12.2. Found: C, 63.2; H, 5.3; N, 12.2.

2-Aminomethyl-6-chloro-3,4-dihydro-4-hydroxy-3-methyl-4-phenylquinazoline (**6a**).

A solution of 3.15 g. (0.01 mole) of **4** in a mixture of 600 ml. of tetrahydrofuran and 100 ml. of 2-propanol was hydrogenated in the presence of Raney nickel for 1 hour. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure to give 1.7 g. (55%) of **6a** as colorless crystals, m.p. 190-192° dec. Recrystallization from a mixture of tetrahydrofuran and methanol afforded the analytical sample; uv (2-propanol) λ max 223 mμ (ε, 15,900) 290 (ε, (11,800); nmr (DMSO): δ 2.82 ppm (s, 3, $N-CH_3$), 3.62 (s, 2, $-CH_2-$), 6.98 (d, 1, J = 2 Hz, C_5-H), 7.1-7.8 (m, 7, aromatic H), exchangeable protons appeared as very broad signal centered between 2 and 3 ppm.

Anal. Calcd. for $C_{16}H_{16}ClN_3O$: C, 63.7; H, 5.3. Found: C, 64.0; H, 5.3.

2-Aminomethyl-6-chloro-3,4-dihydro-4-methoxy-3-methyl-4-phenylquinazoline (**6b**).

A solution of 3.2 g. (0.01 mole) of **5b** in 100 ml. of tetrahydrofuran and 50 ml. of methanol was hydrogenated over Raney nickel for 2 hours. The catalyst was separated by filtration through Celite and the filtrate was evaporated. The residual oil was dissolved in ether and titrated with methanolic hydrogen chloride. The crystalline hydrochloride (2.5 g.) was collected as

pinkish needles, m.p. 182-184° dec. The analytical sample was recrystallized from a mixture of methanol and ether to give white needles, m.p. 185-187° dec.; uv (2-propanol) λ max 225 mμ (ε, 19,000) 286 (ε, 13,140) infl 310 (ε, 5,420); nmr (DMSO): δ 2.73 (s, 3, CH_3), 2.96 (s, 3, CH_3), 4.16 (s, 2, $-CH_2-$), 6.73 (d, 1, J = 2 Hz, C_5-H), 7-7.6 (m, 7, aromatic H), 8.6 (broad s, 3, NH_3^+).

Anal. Calcd. for $C_{17}H_{19}Cl_2N_3O$: C, 57.9; H, 5.4; N, 11.9. Found: C, 57.4; H, 5.4; N, 11.8.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (**7**) (3).

A.

A solution of 1 g. of **6a** in 20 ml. of glacial acetic acid was heated under reflux for 5 minutes. The solvent was evaporated and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The methylene chloride layer was separated, dried and evaporated. Crystallization of the residue from methylene chloride/ether yielded 0.65 g. (69%) of **7**, m.p. and m.m.p. with an authentic sample (3) 243-246°.

B.

A solution of **6b** and 0.25 g. of sodium acetate in 20 ml. of glacial acetic acid was heated under reflux for 5 minutes. After evaporation, the residue was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was separated, dried and evaporated. Crystallization of the residue from methylene chloride/ether yielded 0.58 g. (71%) of **7**, m.p. and m.m.p. as above.

C.

The crude product obtained by hydrogenating 1.75 g. (0.005 mole) of **5c** with Raney nickel in 125 ml. of tetrahydrofuran and 10 ml. of ethanol was refluxed in 25 ml. of acetic acid for 5 minutes. After evaporation, the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate. The organic layer was separated, dried and evaporated. Crystallization of the residue from methylene chloride/ether gave 0.65 g. (45%) of **7**, m.p. and m.m.p. as above.

Acid Hydrolysis of **2**.

A solution of 2 g. of **2** in 50 ml. of tetrahydrofuran was treated with 50 ml. of 1 *N* hydrochloric acid (8). After sitting at room temperature for 15 minutes, the reaction mixture showed no more nitroso compound on the thin layer chromatogram and was made alkaline by the addition of sodium carbonate solution. The tetrahydrofuran was removed under reduced pressure and the remaining suspension was extracted with a mixture of methylene chloride/ethanol 9:1. The extracts were dried over sodium sulfate and evaporated. The residue was dissolved in 20 ml. of methylene chloride and was allowed to crystallize. A small amount of methylene chloride insoluble material separated. It was collected and the filtrate was chromatographed over 45 g. of silica gel (merck 70-325 mesh) using methylene chloride/ethyl acetate 1:3 (v/v) and ethyl acetate/ethanol 9:1(v/v) as the eluants.

The first crystalline compound eluted corresponded to the methylene chloride insoluble material. Recrystallization of the combined crops from tetrahydrofuran/2-propanol yielded 0.25 g. (14%) of compound **4**, m.p. 195-198° dec. The next compound eluted was crystallized from methylene chloride/hexane and was found to be identical with compound **3** (3), yield, 0.56 g. (32%).

The third component eluted with the more polar solvent mixture was crystallized from methylene chloride/hexane to yield 0.58 g. (32%) of compound **1**.

Alkaline Hydrolysis of **2**.

A solution of 1 g. of *N*-nitrosochlordiazepoxide in 25 ml. of tetrahydrofuran and 25 ml. of methanol was treated with 50 ml. of 1 *N* sodium hydroxide solution. After sitting at room temperature for 15 minutes, the mixture was buffered by the addition of sodium bicarbonate, partially evaporated under reduced pressure and extracted with methylene chloride. The extracts were dried over sodium sulfate and evaporated. The residue was crystallized from methylene chloride/hexane to yield 0.71 g. (81%) of compound **3**, m.p. 239-241° dec.

Acknowledgement.

The authors are grateful to the Physical Chemistry Department under the direction of Dr. R. P. W. Scott in particular to Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, Mr. S. Traiman for the ir spectra, Dr. W. Benz for the mass spectra, and Dr. V. Toome for the uv spectra. One of the authors, M. C. Archer, is indebted to NIEHS for grant 1-PO1-ES00597.

REFERENCES

(1) Paper LXIV, Leo H. Sternbach, F. D. Sancilio and John F. Blount, *J. Med. Chem.*, 17, 374 (1974).

(2) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 1111 (1961).

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

(4) Reaction of the nitrosoamidine with other nucleophiles will be reported at a later date.

(5) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, 89, 1147 (1967).

(6) Melting points were determined in a capillary melting point apparatus. The uv spectra were measured on a Cary Model 14 spectrophotometer, nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer.

(7) Nitrosation of 3.3 g. (0.01 mole) of **1** with 0.77 g. (0.011 mole) of sodium nitrite in 200 ml. of 0.1 *N* hydrochloric acid for 24 hours at room temperature yielded 31% of compound **4** and 50% of starting material. None of the nitroso compound **2** could be detected by thin layer chromatography.

(8) Hydrolysis of **2** with 0.2 *N* hydrochloric acid at room temperature for 2 hours yielded 63% of compound **3** and 25% of compound **1**.