THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 2

JANUARY 24, 1975

# Quinazolines and 1,4-Benzodiazepines. LXVI.[1] Reactions of a Nitrosoamidine with Nucleophiles

A. Walser* and R. Ian Fryer

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

*Received April 12, 1974*

*N*-Nitroso chloro diazepoxide **2** was found to react with a variety of nucleophilic reagents to yield 2-substituted benzodiazepines and diazomethane. This novel reaction was used for the synthesis of the 2-alkoxybenzodiazepines **3**, the 2-hydrazinobenzodiazepines **4** and **5**, the 2-aziridino derivative **6**, the 2-ethylthiobenzodiazepine **11**, the 2-oximinobenzodiazepines **12**, the 2-guanidino derivative **13**, and the 2-malonyl derivatives **14**. Reduction of the nitrosoamidine **2** with lithium aluminum hydride gave the known 4-hydroxybenzodiazepine **15**.

In a recent publication we reported that the nitrosoamidine group in compound **2** can be readily hydrolyzed under basic conditions to give the lactam **1**.[1] As a continuation of this work it has been found that the nitrosoamidine group is readily replaced by a variety of nucleophiles. For example, nucleophilic reagents such as alkoxides, basic amines, and carbanions all effectively replace the nitrosoamidine function in compound **2**. In this manner the facile synthesis of a number of unusual 2-substituted benzodiazepines has been accomplished.

Treatment of the nitrosoamidine **2** with methanol and sodium methoxide at room temperature or with methanol and triethylamine at reflux, led to the imino ether **3a**[2] in nearly quantitative yield. This efficient synthesis of imino ethers under alkaline conditions was especially useful for the preparation of the allylic ether **3b** and the basic ether **3c** (see Scheme I).

Some examples of the use of basic amines as nucleophiles are given by the reaction of hydrazines, hydroxylamines, aziridine, and guanidine with the nitrosoamidine. The reaction with hydrazine proceeded well at room temperature and afforded the known 2-hydrazinobenzodiazepine **4**.[3] Compound **4** was converted by standard techniques into the acetyl derivative **7**. This compound was also obtained together with the triazolobenzodiazepine **10** [4]when the nitrosoamidine **2** was treated with acetylhydrazine. Methylhydrazine attacked the nitrosoamidine **2** predominantly with the more nucleophilic methylated nitrogen and formed compound **5**. The position of the methyl group on the hydrazine was confirmed by the conversion of **5** into the hydrazone **8** on treatment with formaldehyde. The reaction of **2** with ethylenimine at room temperature produced mainly the aziridinobenzodiazepine **6**. Under the more vigorous conditions of refluxing in ethylenimine, the only prodct isolated was compound **9**. The formation of higher "homologs" was not observed under these conditions. It should be pointed out that the aziridine protons of compound **6** appear as a sharp singlet in the nmr spectrum, but in compound **9** where the nitrogen inversion must be quite slow, possibly due to hydrogen bonding, the aziridine protons appear as an $A_2B_2$ system. The flipping of the diazepine ring seems to be fairly rapid since none of the nmr spectra given in the Experimental Section showed AB systems for the $C_3$ protons but singlets of varying broadness.

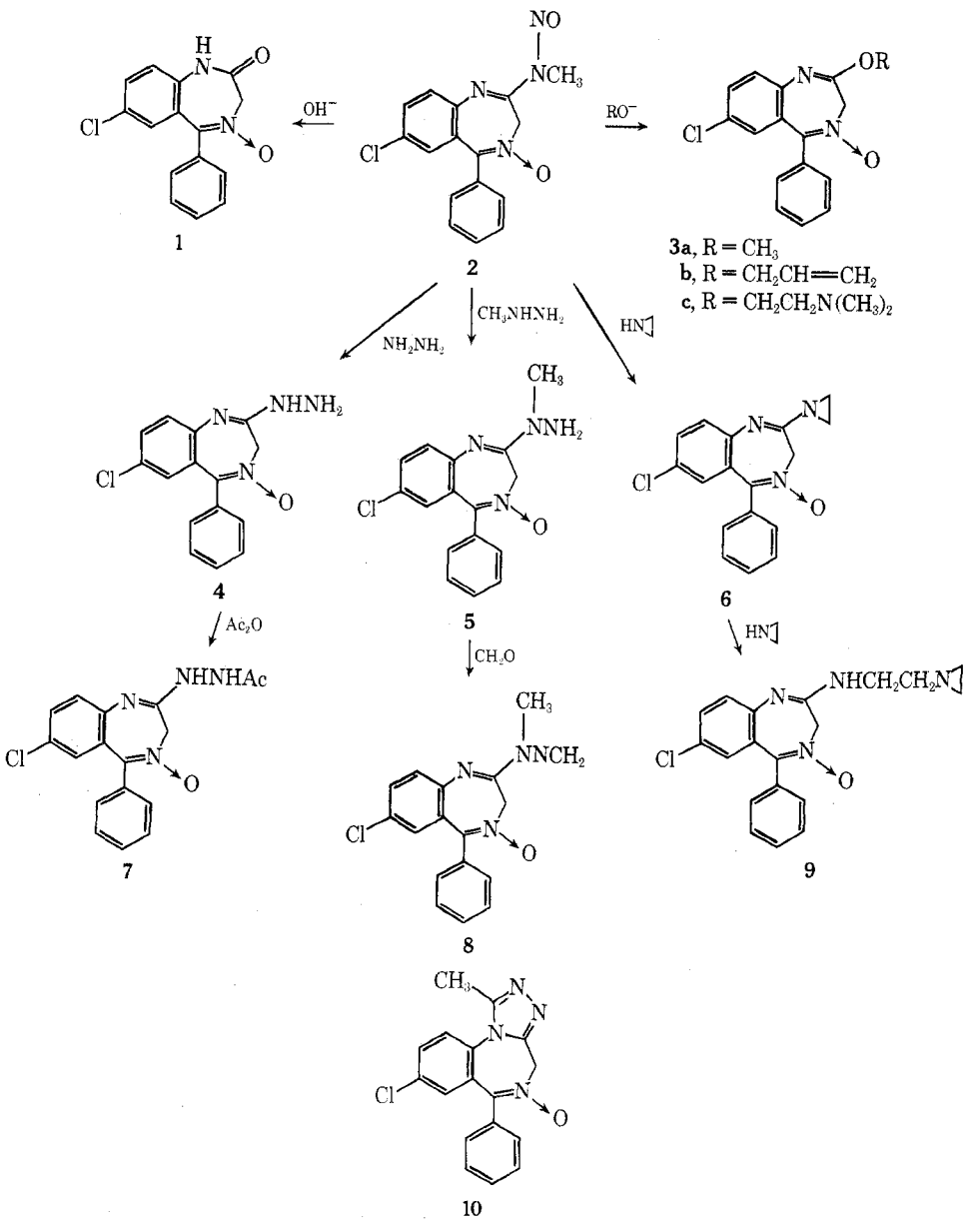
Hydroxylamines also reacted readily with the nitrosoamidine group and led to the formation of compounds **12a** and **12b** (see Scheme II). The spectroscopic data were considered to be more compatible with the assignment of the amidoxime structure rather than with the hydroxyamidine, bearing the double bond in the ring. The 4-deoxy derivative corresponding to **12a** has previously been prepared[5] by reaction of the benzodiazepine-2-thione with hydroxylamine. Since the 2-thione 4-oxide cannot be prepared by the normal route, which would consist of the reaction of **1** with phosphorus pentasulfide, the method *via* the nitrosoamidine obviously has a considerable advantage. The unavailability of the 2-thione 4-oxide was probably also the reason that the thioether **11** has not been described earlier. Compound **11** was obtained by treatment of the nitrosoamidine with potassium ethylthiolate. As expected reaction of **2** with guanidine afforded compound **13**.

The nitrosoamidine also underwent smooth reactions with the carbanions of dimethyl malonate and malononitrile. While the anion of malononitrile reacted at room temperature, the reaction with potassium dimethyl malonate required more vigorous conditions. The spectral data of the products **14a** and **14b** are in agreement with the indicated structures. In the nmr spectra the large chemical shift (11.5 ppm) of the proton on the nitrogen in the 1 position can be explained as being due to hydrogen bonding. The reduction of **14a** and **14b** with phosphorus trichloride led to the corresponding 4-deoxy derivatives **16a** and **16b** while lithium aluminum hydride reduced the nitrosoamidine as expected to the known hydroxylamine **15**.[6]

## Experimental Section

Melting points were determined in a capillary melting point apparatus and are not corrected. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument in deuteriochloroform or deuteriodimethyl sulfoxide with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

**Scheme I**




**7-Chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3a).**[2] **A.** Potassium *tert*-butoxide (1 g, 9 mmol) was added to a solution of 10 g (0.03 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**)[1] in 50 ml of ether and 50 ml of methanol. After stirring for 30 min at room temperature, the mixture was partially evaporated. The crystalline material was collected and washed with methanol–water and with methanol to leave 7.9 g of product with mp 186–188°. From the mother liquor another batch of 0.7 g with the same melting point was obtained; yield 8.6 g (94%).

**B.** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 50 ml of methanol, and 5 ml of triethylamine was refluxed for 10 min. The solvents were evaporated under reduced pressure, and the residue was crystallized from methanol to leave 2.6 g (86%) of product with mp 188–187°.

**2-Allyloxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3b).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 50 ml of tetrahydrofuran, 5 ml of allyl alcohol, and 0.3 g (2.7 mmol) of potassium *tert*-butoxide was stirred at room temperature for 15 min. The solvents were removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate solution and benzene. The benzene layer was separated, dried over sodium sulfate, and evaporated. Crystallization of the residue from ether yielded 1.6 g (49%) of product with mp 118–120°. The analytical sample was recrystallized from acetone–hexane: mp 120–122°; nmr ($CDCl_3$) $\delta$ 4.5 (s, 2, $C_3$–H), 4.8 (d with fine structure, 2, $OCH_2$), 5.1–6.5 (m, 3, olefinic H), 6.9–7.8 ppm (m, 8, aromatic H); uv $\lambda_{max}$ 245 m$\mu$ ($\epsilon$ 25,550), 255 (25,700), 310 (10,400).

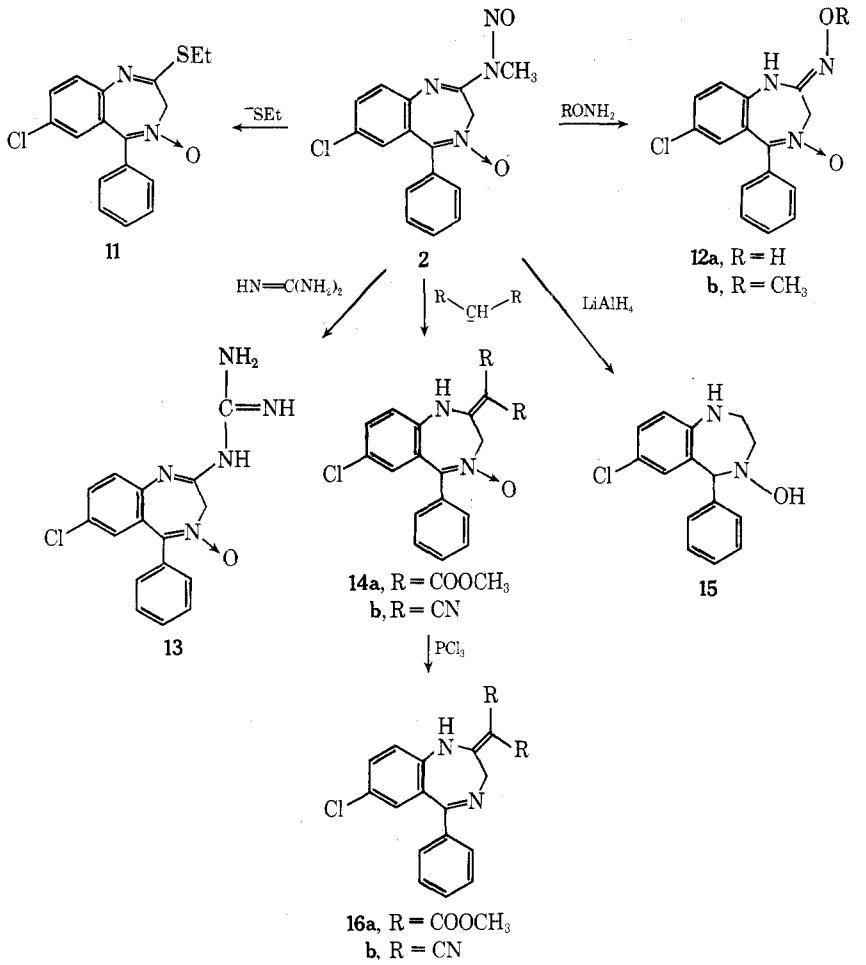
*Anal.* Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57 Found: C, 66.16; H, 4.51; N, 8.63.

**7-Chloro-2-(2-dimethylaminoethoxy)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3c).** A mixture of 6.6 g (0.02 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, 80 ml of tetrahydrofuran, 10 ml of 2-dimethylaminoethanol, and 0.8 g (7 mmol) of potassium *tert*-butoxide was allowed to stand at room temperature for 16 hr. The solvent was evaporated under reduced pressure and the residue was partitioned between benzene and saturated aqueous sodium bicarbonate solution. The benzene layer was dried over sodium sulfate and evaporated under reduced pressure at the end azeotropically with xylene to remove the rest of 2-dimethylaminoethanol. The residue was chromatographed over 200 g of silica gel which had been treated with 10% (v/v) triethylamine in acetone. The pure fractions eluted with acetone were combined and evaporated. Crystallization from ether–hexane yielded 3 g (42%) of product with mp 105–110°. For analysis it was recrystallized from ether: nmr ($CDCl_3$) $\delta$ 2.34 [s, 6, $N(CH_3)_2$], 2.7 (t, 2, $J$ = 6 Hz, N–$CH_2$–), 4.42 (t, 2, $J$ = 6 Hz, O–$CH_2$–), 4.53 (s, 2, $C_3$–H), 7–7.8 ppm (m, 8, aromatic H); uv $\lambda_{max}$ 245 m$\mu$ ($\epsilon$ 25,300), 252 (25,400), 310 (10,200).

*Anal.* Calcd for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.63; H, 5.74; N, 11.75.

**7-Chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-**

**Scheme II**




**Oxide (4).**[3] A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 30 ml of tetrahydrofuran, 30 ml of methanol, and 3 ml of hydrazine was allowed to sit at room temperature for 1 hr. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride–ether yielded 2.5 g (83%) of yellow product with mp 288–290° (the melting point reported in the literature[3] is considerably lower): nmr (DMSO) $\delta$ 4.46 (broad s, 2, $C_3$–H), 6.78 (m, 1, $C_6$–H), 7.2–7.7 ppm (m, 7, aromatic H) (the exchangeable protons appear very broad with undefined chemical shift); uv (2-PrOH) $\lambda_{max}$ 244 m$\mu$ ($\epsilon$ 52,500), 267 (48,800), infl 310 (20,100), infl 360 (4300); mass spectrum *m/e* 300 ($M^+$).

*Anal.* Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 59.85; H, 4.25; N, 18.38.

**7-Chloro-2-(1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (5).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, 30 ml of tetrahydrofuran, 30 ml of methanol, and 3 ml of methylhydrazine was allowed to sit at room temperature for 16 hr.

The solvents were evaporated under reducted pressure and the residue was crystallized from methylene chloride–ether to yield 1.8 g (57%) of light yellow crystals with mp 218–221° dec.

The analytical sample was recrystallized from methylene chloride–2-propanol: mp 220–222° dec; nmr (DMSO-*d*) $\delta$ 3.34 (s, 3, $NCH_3$), 5.05 (broad s, 2, $NH_2$) ($C_3$ protons appear as very broad absorption between 4.2 and 5.6 ppm), 6.77 (d, 1, $J$ = 2 Hz, $C_6$-H), 7.1 (d, 1, $J$ = 8 Hz, $C_9$-H), 7.35 (q, 1, $J_{AB}$ = 8 Hz, $J_{AX}$ = 2 Hz, $C_8$-H), 7.45 (s, 5, $C_6H_5$); uv $\lambda_{max}$ 246 m$\mu$ ($\epsilon$ 25,500), 274 (34,200), sh 355 (2700).

*Anal.* Calcd for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.08; H, 4.78; N, 17.91.

**7-Chloro-2-(2-methylene-1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (8).** A mixture of 1 g (3.2 mmol) of 7-chloro-2-(1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**5**), 50 ml of ethanol, and 0.5 ml of aqueous formaldehyde (30%) was heated on the steam bath for 5 min. After concentration down to half of the volume the product crystallized upon cooling. The colorless crystals were collected (0.9 g, 86%) and recrystallized from ethanol for analysis: mp 240–242° dec; nmr ($CDCl_3$) $\delta$ 3.44 (s, 3, $NCH_3$) ($C_3$ protons appear as very broad signal centered at *ca.* 5.2 ppm), 6.47 (d, 1) and 6.68 (d, 1) (AB system, $J$ = 11 Hz, $=CH_2$), 7–7.9 ppm (m, 8, aromatic H); uv $\lambda_{max}$ 247 m$\mu$ ($\epsilon$23,000), 284 (43,350), infl 360 (2500).

*Anal.* Calcd for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.40; H, 4.48; N, 17.06.

**2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (7). A.** Acetic anhydride (1.5 ml) was added to a solution of 2.5 g of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**3**) in 50 ml of methylene chloride. After stirring for 15 min at room temperature, the mixture was concentrated and crystallized by addition of ether to yield 2.6 g (91%) of product. The analytical sample was recrystallized from dimethylformanide: mp 272–275°; uv $\lambda_{max}$ 244–245 m$\mu$ ($\epsilon$26,800), 268–269 (30,500), infl 315 (8300), infl 350 (2800).

*Anal.* Calcd for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.35. Found: C, 59.26; H, 4.60; N, 16.34.

**B.** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 30 ml of ethanol, 3 ml of triethylamine, and 2 g of acetylhydrazine was refluxed for 24 hr. The solvent was evaporated and replaced by 1-butanol and refluxing was continued for another day. The residue obtained after evaporation was crystallized from methylene chloride. The crystals were collected and recrystallized from methylene chloride–ethanol to leave 1.85 g of product with mp 265–270° dec. The filtrate was chromatographed over 70 g of silica gel using 10% ethanol in methylene chloride. Beside an additional amount of 0.11 g of product **7** (total yield 57%), 0.31 g (9.5%) of 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,5-*a*][1,4]benzodiazepine 5-oxide (**10**)[4] was also obtained.

**2-(1-Aziridino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (6).** Aziridine (15 ml) was added to a solution of 10 g (0.03

mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**) in 100 ml of dry tetrahydrofuran. After stirring for 5 hr at room temperature under a stream of nitrogen, the solvent was removed under reduced pressure and the residue was crystallized from ether–hexane to yield 5.7 g of product with mp 135–140°.

It was further purified by chromatography over 100 g of silica gel using methylene chloride–ethyl acetate 1:1 (v/v). The pure product was crystallized from ether: mp 136–138°; nmr ($CDCl_3$) 2.43 [s, 4, $N(CH_2)_2$], 4.55 (s, 2, $C_3$-H), 6.9–7.8 ppm (m, 8, aromatic H); uv $\lambda_{max}$ 239 mμ (ε 27,800), 272 (28,400), infl 310 (9200).

*Anal.* Calcd for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.52; N, 13.47. Found: C, 65.39; H, 4.49; N, 13.44.

**2-[2-(1-Aziridino)ethylamino]-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (9).** A mixture of 10 g (0.03 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**) and 30 ml of aziridine was stirred for 10 min under a stream of nitrogen. The escaping diazomethane was destroyed by bubbling through a solution of acetic acid in ether. After heating to reflux for 5 min, the reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and evaporated.

Crystallization of the residue from ether yielded 8.6 g (80%) of product with mp 160–162°. For analysis it was recrystallized from methylene chloride–ether: mp 163–165°; nmr (DMSO-*d*) δ 1.1 (m, 2) and 1.53 [m, 2, $A_2B_2$ system, $N(CH_2)_2$], 2.32 (t, 2, $J$ = 6.5 Hz, $-CH_2-N$), 3.4 (q, 2, $J$ = 6 Hz, $-NHCH_2-$), 4.4 (broad s, 2, $C_3$-H), 6.7 (d, 1, $J$ = 2 Hz, $C_6$-H), 7.05 (d, 1, $J$ = 8.5 Hz, $C_9$-H), 7.1–7.6 (m, 6, $C_6H_5$ and $C_8$-H), 8.06 ppm (t, 1, $J$ = 5.5 Hz, NH); uv $\lambda_{max}$ 224 mμ (ε 28,600), 267 (33,150), infl 315 (7300), infl 355 (2900).

*Anal.* Calcd for $C_{19}H_{19}ClNO_4O$: C, 64.31; H, 5.40; N, 15.79. Found: C, 64.36: H, 5.55; N, 16.00.

**7-Chloro-5-phenyl-2-ethylthio-3*H*-1,4-benzodiazepine 4-Oxide (11).** A mixture of 16.5 g (0.05 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 25 ml of ethanethiol, 150 ml of tetrahydrofuran, and 1 g of potassium *tert*-butoxide was stirred for 20 min with cooling in ice–water. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and benzene. The benzene layer was dried and evaporated. Chromatography of the residue on 250 g of silica gel using 10% ethyl acetate in methylene chloride and crystallization of the clean fractions from methylene chloride–ether–hexane yielded 4.7 g (28%) of product with mp 142–144°: nmr ($CDCl_3$) δ 1.27 (t, 3, $J$ = 7 Hz $-CH_3$), 3.14 (q, 2, $J$ = 7 Hz, $S-CH_2$), 4.43 (s, 2, $C_3$-H), 7.03 (m, 1, $C_6$-H), 7.2–7.9 ppm (m, 7, aromatic H); uv λ infl 224 mμ (ε 18,800), max 246 (21,400), 284 (32,050), infl 320 (9700).

*Anal.* Calcd for $C_{17}H_{15}ClN_2OS$: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.54; H, 4.63; N, 8.41.

The major product of the reaction (7.5 g) was identified as 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

**7-Chloro-2,3-dihydro-2-hydroxyimino-5-phenyl-1*H*-1,4-benzodiazepine 4-Oxide (12a).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 35 ml of ethanol, 5 ml of triethylamine, and 3 g of hydroxylamine hydrochloride was heated to reflux for 20 min. The product was crystallized by addition of water. It was dissolved in methylene chloride–ethanol. The solution was dried over sodium sulfate and evaporated. Crystallization from methylene chloride–ethanol yielded 2.2 g (73%) of product with mp 250–255° dec: nmr (DMSO-*d*) δ 4.51 (broad s, 2, $C_3$-H), 6.75 (m, 1, $C_6$-H), 7.2–7.6 (m, 7, aromatic H), 9.5 (s, 1, OH or NH), 10.2 ppm (s, 1, OH or NH); uv $\lambda_{max}$ 240 mμ (ε 29,000), infl 279 (17,900), infl 310 (10,000), infl 360 (2800); ir (KBr) 1660 $cm^{-1}$ (C=N–OH).

*Anal.* Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.00; N, 13.93. Found: C, 59.47; H, 4.16; N, 13.80.

**7-Chloro-2,3-dihydro-2-methoxyimino-5-phenyl-1*H*-1,4-benzodiazepine 4-Oxide (12b).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-2*H*-1,4-benzodiazepine 4-oxide (**2**), 35 ml of triethylamine, and 3 g of methoxyamine hydrochloride was refluxed for 16 hr. The crystals precipitated by addition of water were collected and recrystallized from methylene chloride–ethanol to yield 2.5 g (79%) with mp 232–234°. The analytical sample was recrystallized from the same solvents: nmr (DMSO-*d*) δ 3.77 (s, 3, $OCH_3$), 4.53 (broad s, 2, $C_3$-H), 6.75 (m, 1, $C_6$-H), 7.2–7.6 (m, 7, aromatic H), 9.6 ppm (s, 1, NH); uv $\lambda_{max}$ 242 mμ (ε 29,600), infl 259 (4400), infl 310 (9600), infl 357 (2600); ir KBr) 1650 $cm^{-1}$ (–C=N–O).

*Anal.* Calcd for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.84; H, 4.40; N, 13.38.

**7-Chloro-2-guanidino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (13).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 30 ml of tetrahydrofuran, 50 ml of *tert*-butyl alcohol, 2 g of guanidine hydrochloride, and 2.3 g of potassium *tert*-butoxide was stirred at room temperature for 3 hr. After evaporation under reduced pressure, the residue was washed with water and dissolved in methylene chloride–ethanol. The solution was dried and evaporated. Crystallization from methylene chloride–ethanol yielded 2 g (61%) of product with mp 245–248° dec. For analysis it was recrystallized from the same solvents: mp 250–252° dec; nmr (DMSO-*d*) δ 4.33 (s, 2, $C_3$-H), 6.8 (d, 1, $J$ = 2 Hz, $C_6$-H), 7.16 (d, 1, $J$ = 8.5 Hz, $C_9$-4), 7.2–7.6 (m, 6, $C_6H_5$ and $C_8$-H), 4 exchangeable protons appear as very broad signal between 7.4 and 10 ppm; uv $\lambda_{max}$ 245 mμ (ε 17,700) 290 (38,600) infl 300 (3400).

*Anal.* Calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37. Found: C, 58.74; H, 4.33; N, 21.38.

**7-Chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (14a).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 20 ml of dimethylformamide, 5 ml of dimethyl malonate, and 1.3 g (0.0115 mol) of potassium *tert*-butoxide was heated to 100–120° for 5 min under a stream of nitrogen. After the addition of 2 ml of glacial acetic acid the cool reaction mixture was partitioned between methylene chloride and water. The methylene chloride layer was washed with water, dried over sodium sulfate, and evaporated. Crystallization from ether yielded 2.75 g (69%) of light yellow product with mp 194–195°. For analysis it was recrystallized from methylene chloride–hexane: nmr ($CDCl_3$) δ 3.78 (s, 3, $OCH_3$), 3.84 (s, 3, $OCH_3$), 4.92 (broad s, 2, $C_3$-H), 7–7.8 (m, 8, aromatic H), 11.6 ppm (s, 1, NH); uv $\lambda_{max}$ 228 mμ (ε 23,500), 304 (38,110), infl 340 (12,500); ir ($CHCl_3$) 3200 (NH), 1720, 1675 $cm^{-1}$ (COOMe).

*Anal.* Calcd for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; N, 6.98. Found: C, 59.78; H, 4.21; N, 6.90.

**7-Chloro-1,3-dihydro-3-(dicyanomethylene)-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (14b).** A mixture of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**), 20 ml of dimethylformamide, 2.3 g (0.035 mol) of malononitrile, and 1.3 g (0.0115 mol) of potassium *tert*-butoxide was stirred at room temperature for 30 min. After the addition of 2 ml of glacial acetic acid the product was crystallized by addition of water. It was collected, washed with water, and recrystallized from methylene chloride–ethanol to leave 2.65 g (79%) with mp 240–242° dec. Nmr indicated these crystals to contain methylene chloride. Other solvents also produced solvates, *e.g.*, 2-propanol and dioxane. A sample recrystallized from dioxane had the same melting point and analyzed well for a hemidioxanate: nmr (DMSO-*d*) 3.57 (s, 4, dioxane), 4.83 (s, 2, $C_3$-H), 6.95 (m, 1, $C_6$-H), 7.2–7.7 (m, 7, aromatic H), *ca.* 11.5 ppm (very broad signal N-H); uv $\lambda_{max}$ 231 mμ (ε 16,750), 303 (35,400), infl 300 (13,700).

*Anal.* Calcd for $C_{18}H_{11}ClN_4O \cdot \frac{1}{2}C_4H_8O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.42; H, 3.93; N, 14.65.

**7-Chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine (16a).** Phosphorus trichloride (4 ml) was added to a solution of 4 g (0.01 mol) of 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine 4-oxide in 100 ml of methylene chloride. After sitting at room temperature overnight the solution was washed with 10% aqueous sodium carbonate solution. The methylene chloride layer was dried and evaporated. Crystallization of the residue from 2-propanol and recrystallization from methylene chloride–2-propanol yielded 3.2 g (83%) of product with mp 138–140°. A different crystalline modification with mp 165–166° was also observed: nmr ($CDCl_3$) δ 3.75 (s, 3, $OCH_3$), 3.85 (s, 3, $OCH_3$), 4.43 (broad s, 2, $C_3$-H), 7.05 (d, 1, $J$ = 8.5 Hz, $C_9$-H), 7.1–7.6 (m, 7, aromatic H), 11.5 ppm (s, 1, NH); uv λ sh 277 mμ (ε 14,000), max 310 (31,200); ir ($CHCl_3$) 3150 (NH), 1720, 1670 $cm^{-1}$ ($COOCH_3$).

*Anal.* Calcd for $C_{20}H_{17}ClN_2O_4$: C, 62.43; H, 4.45; N, 7.28. Found: C, 62.68; H, 4.47; N, 7.11.

**7-Chloro-1,3-dihydro-2-(dicyanomethylene)-5-phenyl-2*H*-1,4-benzodiazepine (16b).** A mixture of 1 g of 7-chloro-1,3-dihydro-2-(dicyanomethylene)-5-phenyl-2*H*-1,4-benzodiazepine 4-oxide (**14b**), 100 ml of methylene chloride, and 1 ml of phosphorus trichloride was stirred at room temperature for 5 hr. The solution was washed with 10% aqueous sodium carbonate solution, dried over sodium sulfate, and evaporated. Chromatography of the residue over 20 g of silica gel using 10% ethyl acetate in methylene chloride and crystallization from tetrahydrofuran–ethyl acetate yielded 0.55 g (58%) of product with mp 274–276°.

*Anal.* Calcd for $C_{18}H_{11}ClN_4$: C, 67.82; H, 3.48; N, 17.58. Found:

C, 67.95; H, 3.40; N, 17.33.

**7-Chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (15).**[6] A solution of 3.3 g (0.01 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2**) in 10 ml of tetrahydrofuran was added to a suspension of 2 g (0.05 mol) of lithium aluminum hydride in 50 ml of ether cooled to −20°. The mixture was stirred at −20 to −15° for 15 min and 10 ml of water was added cautiously. The inorganic material was separated by filtration; the filtrate was dried over sodium sulfate and evaporated. Crystallization of the residue from 2-propanol yielded 2.2 g of product with mp and mmp 167–169°.

**Acknowledgment.** The authors wish to thank the following members of our Physical Chemistry Department under the direction of Dr. R. Scott: Dr. F. Scheidl and his staff for the microanalysis, Dr. W. Toome for the uv spectra, and Mr. S. Traiman for the ir spectra.

**Registry No.**—**2**, 51715-17-4; **3a**, 3897-18-5; **3b**, 53216-78-7; **3c**, 53216-79-8; **4**, 18091-88-8; **5**, 53260-30-3; **6**, 53216-80-1; **7**, 18084-62-3; **8**, 53216-81-2; **9**, 53216-82-3; **11**, 53216-83-4; **12a**, 51483-10-4; **12b**, 51483-05-7; **13**, 53216-84-5; **14a**, 53216-85-6; **14b**, 53216-86-7; **14b** hemidioxonate, 53216-87-8; **15**, 1803-98-1; **16a**, 53216-88-9; **16b**, 53216-89-0; methanol, 67-56-1; allyl alcohol, 107-18-6; 2-dimethylaminoethanol, 108-01-0; hydrazine, 302-01-2; methylhydrazine, 60-34-4; formaldehyde, 50-00-0; acetic anhydride, 108-24-7; acetylhydrazine, 1068-57-1; aziridine, 151-56-4; ethanethiol, 75-08-1; hydroxylamine hydrochloride, 5470-11-1; methoxyamine hydrochloride, 593-56-6; guanidine hydrochloride, 15827-40-4.

## References and Notes

(1) Paper LXV: A. Walser, R. Ian Fryer, L. H. Sternbach, and M. Archer, *J. Heterocycl. Chem.*, **11**, 619 (1974).
(2) (a) Netherlands Patent Appl. 6,412,484 (Hoffmann-La Roche & Co., AG); (b) Netherlands Patent Appl. 6,412,300 (Hoffmann-La Roche & Co., AG).
(3) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).
(4) Netherlands Patent Appl. 6,916,543 (Takeda Chemical Ind., Ltd.).
(5) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971).
(6) E. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **28**, 2457 (1963).

# Quinoxaline 1,4-Dioxides. Substituent Effects on the Reaction of Benzofurazan 1-Oxides with Carbonyl Compounds[1a]

Elie Abushanab* and Nicholas D. Alteri, Jr.[1b]

*Department of Medicinal Chemistry, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island 02881*

*Received August 19, 1974*

Two types of reactions were used to study the effect of substituents ($CH_3$, $OCH_3$, and $CO_2CH_3$) on the condensation of 5(6)-substituted benzofurazan 1-oxides with acetonyl methyl sulfide (BFO reaction, A), and 4-substituted *o*-quinone dioximes with pyruvaldehyde (OQD reaction, B). Each reaction allowed the isolation of only one of the two possible isomers and the study of its nmr properties. The nitrogen atom is an electrophile in reaction A and a nucleophile in reaction B. Thus the same substituent is expected and does favor the formation of opposite ratios of 6:7 isomeric substituted quinoxaline hydroxamic acid esters **4**. The ratios were determined from nmr spectra of these esters where the chemical shifts of the H-5 and H-8 protons, unlike their counterparts in quinoxaline 1,4-dioxides, are assignable. The results are interpreted by assuming that benzofurazan 1-oxides react in their ortho dinitroso tautomeric forms.

A few years ago, an elegant method for the preparation of quinoxaline 1,4-dioxides was reported. It involved a condensation of benzofurazan 1-oxide (BFO) with either enamines or enolate anions.[2,3] Although the exact mechanism was not elucidated, initial attack at either one of the two nitrogen atoms of BFO followed by cyclization with concomitant elimination of amines, in the former, and water, in the latter, would explain the experimental results. Partial support for this mechanism came from the isolation of dihydroquinoxaline 1,4-dioxide which is a suggested intermediate in the above mechanism.[4]

Only one quinoxaline 1,4-dioxide can be obtained when a carbonyl compound, which under the reaction conditions forms one enolic form, is condensed with unsubstituted BFO. However, a mixture of 6- and 7-substituted quinoxaline 1,4-dioxide isomers is expected when 5(6)-substituted BFO's are used. Indeed such a case has been reported when 5(6)-trifluoromethyl BFO was condensed with acetyl acetone.[5]

Contradictory reports concerning reactions of other 5(6)-substituted BFO's with various ketones have also appeared. While Haddadin and coworkers claimed the formation of mixture of isomers when the 5(6)-substituted BFO's (**1a**, **1b**, and **1d**) were condensed with benzoylacetophenone,[6] Mason and Tennant reported the isolation of only the 7-substituted quinoxaline 1,4-dioxide when BFO's (**1b**, **1d**, and **1e**) were allowed to react with benzoylacetonitrile.[7] Later results partially supported the above claims. While the condensation of β-keto esters with 5(6)-chloro-BFO (**1d**) was found to give a mixture of the corresponding 6- and 7-chloroquinoxaline 1,4-dioxides, 5(6)-methoxy-BFO (**1b**) furnished the 7-methoxy isomer only.[8] In the present work a rigorous study of isomer formation was made in which the electronic effects of a 5(6) substituent on the course of BFO reaction with acetonyl methyl sulfide is reported.

Determination of isomer ratios in 6(7)-substituted quinoxaline 1,4-dioxides is not an easy task since both isomers have very similar spectral and chromatographic properties. Their conversion to other derivatives where H-5 and H-8, unlike their counterparts in the parent compounds, are in different chemical environment allows full structural determination by nmr. Such a conversion has been reported earlier when 2-cyano-3-phenyl-7-substituted quinoxaline 1,4-dioxides were treated with sodium ethoxide to furnish the corresponding hydroxamic acids.[7] In the present compounds (**2a**, **2b**, and **2c**) treatment with aqueous potassium hydroxide furnished the highly insoluble hydroxamic acids (**3**) followed by conversion to the esters (**4**) made possible their structural assignment by examining the aromatic region in the nmr spectra (Scheme I). Unlike the earlier method, these ompounds have no other aromatic protons which could complicate spectral analyses.

Scheme I depicts two types of reactions (A and B) used to determine substituent effects; a BFO reaction (A) in which the nitrogen atom is an electrophile, and a condensa-