Quinazolines and 1,4-Benzodiazepines. XCIII. (1). Synthesis of Imidazo[1,5-*a*][1,4]benzodiazepines from Nitrooximes

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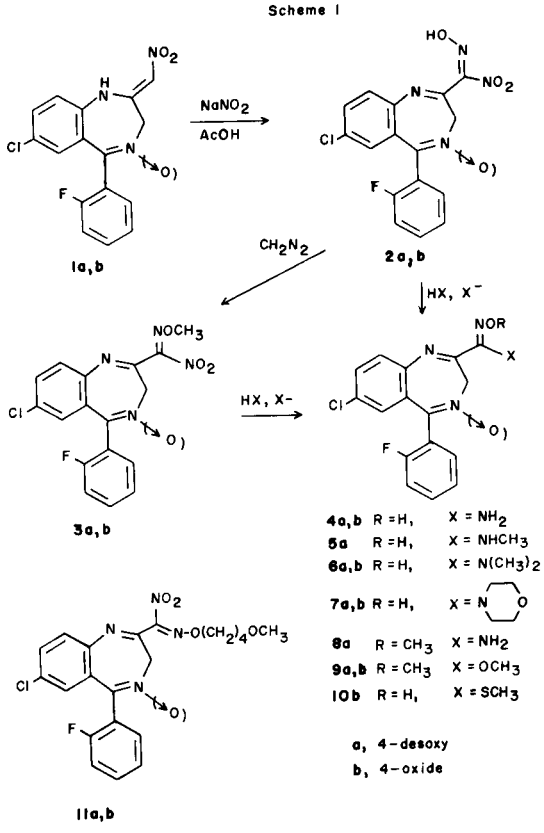
Received October 20, 1982

The displacement of the nitro group in nitrooximes by other nucleophiles was used to prepare various 2-(hydroxyimino)methyl- and 2-(methoxyimino)methyl-1,4-benzodiazepines. These compounds were converted to imidazo[1,5-*a*][1,4]benzodiazepines bearing a tertiary amine, methoxy or thiomethyl group in the 3-position.

J. Heterocyclic Chem., **20**, 551 (1983).

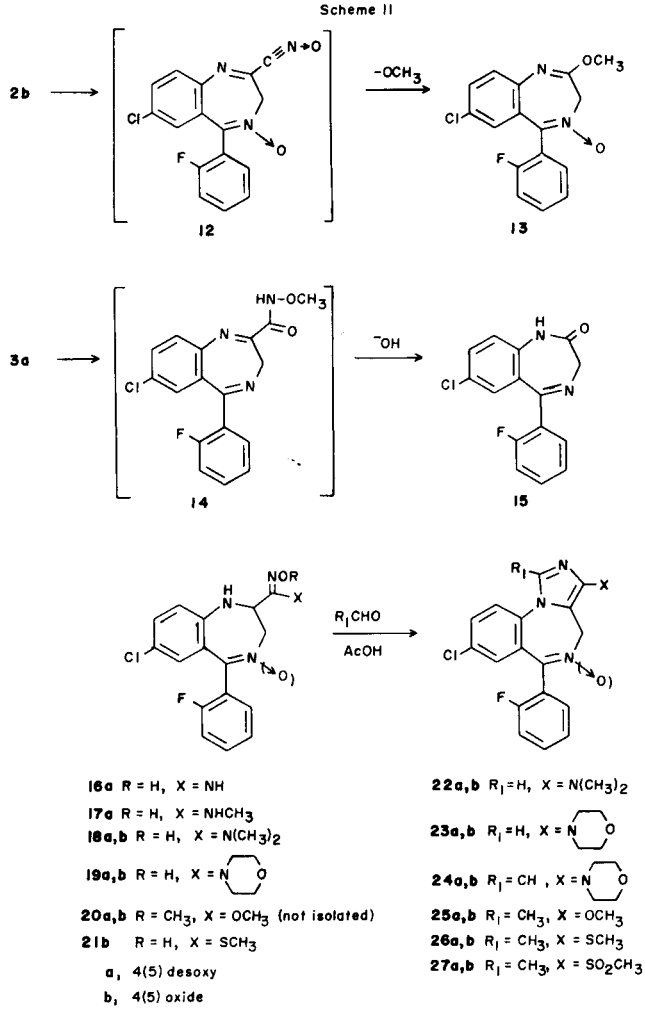
The nitro compounds **1** (2,3) (Scheme I) were shown to be useful precursors for the synthesis of imidazo[1,5-*a*]-[1,4]benzodiazepines (2). We wish to report now the conversion of these nitro compounds to various new benzodiazepines by employing the nitrooximes **2** which were obtained in good yield by nitrosation of **1** with sodium nitrite in glacial acetic acid. The nitro group in these nitrooximes behaves as a leaving group and can be displaced by nucleophiles. A similar reactivity of the nitro group was reported by Wade (4) for 3-nitro-2-isoxazoline and 3-nitro-5,6-dihydro-4H-1,2-oxazine. The oxime methyl ethers **3** were obtained by methylation of **2** with diazomethane. Both **2** and **3** reacted at room temperature with a variety of amines to give the amidoximes **4-8**.

Scheme I



The reaction of **2b** with sodium methoxide in methanol unexpectedly yielded the 2-methoxybenzodiazepine **13** (Scheme II), while the corresponding methyl ether **3b**, under identical conditions, reacted in the anticipated fashion to give **9b**. This different course of the reaction may be due to the formation of the intermediate nitrile oxide **12** from **2b**. Formation of the nitrile oxide **12** is not possible from **3b**. 2-Cyano-1,4-benzodiazepines have been shown to react with methanol to give 2-methoxy derivatives (5).

Scheme II

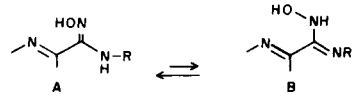


Unlike methoxide, methylthiolate in tetrahydrofuran displaced the nitro group cleanly from **2b** and led to the methylthio oxime **10b**.

We also attempted to prepare the methoxyamide **14** by displacing the nitro group of **3a** with hydroxide. When this reaction was carried out in methanol with aqueous sodium hydroxide, the methoxy oxime **9a** was the major product formed. This is in agreement with the fact that methoxide is a better nucleophile than hydroxide. Reaction of **3a** with aqueous potassium hydroxide in 2-propanol or dimethyl sulfoxide led to the lactam **15**. It is feasible that **14** may be the primary reaction product but suffers further transformation to the lactam **15** under these conditions.

During the methylation of **2** with diazomethane in tetrahydrofuran/ether an interesting side reaction was observed. Beside the major product **3** a more polar by-product was formed and isolated by chromatography. The spectroscopic and analytical data indicated that tetrahydrofuran did participate in the formation of the byproducts **11**. Apparently diazomethane reacted with tetrahydrofuran to form a methyl oxomium ion which alkylated the oxime. The polarity of **11** made us favor the nitrone structure resulting from *N*-alkylation of the oxime but an X-ray crystallographic analysis of **11a** determined that *O*-alkylation had occurred.

Primary and secondary amidoximes of partial structure **A** (R = H, alkyl) may exist in equilibrium with the tautomer **B**. The nmr spectrum of the amidoxime **5** exhibited a doublet for the methyl group and a corresponding quartet for the NH proton. This shows clearly that **5** exists as the tautomer **A** (R = CH_3) and that hydrogen shift to tautomer **B** does not occur readily. **A** is most likely thermodynamically more stable than **B**.

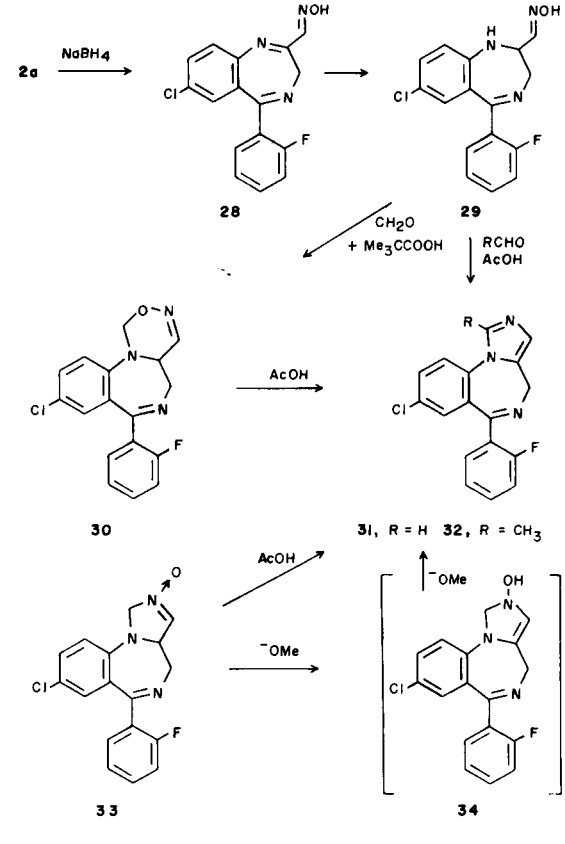


It was possible to selectively reduce the 1,2-imine bond in compounds **4-10** with sodium borohydride in ethanol/tetrahydrofuran and arrive at the dihydro derivatives **16-21** (Scheme II). These compounds have the correct oxidation level to be converted to imidazobenzodiazepines by condensation with aldehydes. Reaction of the dihydro-1,4-benzodiazepines **18-21**, in which **X** contains no exchangeable hydrogens, with formaldehyde or acetaldehyde in glacial acetic acid led indeed to the corresponding imidazo[1,5-*a*][1,4]benzodiazepines **22-26** with yields up to 60%. The nitrone function was reduced to the imine either with phosphorus trichloride or by hydrogenation over Raney nickel. Treatment of the methylthio derivative **26b** with *m*-chloroperbenzoic acid gave the sulfone **27b** which was reduced to **27a** by means of phoshorus trichloride.

The imidazole synthesis described above was also applied to the preparation of midazolam (**32**)(2). The required aldoxime **29** was found to be accessible by treatment of the nitrooxime **2a** with sodium borohydride. The conversion of **2a** to **29** involves two separate steps as shown by thin layer chromatography. In the first reaction step, the nitro group in **2a** is displaced by hydride to yield the previously described **28** (2) which is then reduced as demonstrated earlier (2) to **29**. Reaction of **29** with acetaldehyde in boiling glacial acetic acid gave midazolam (**32**) in 60% yield. Under milder conditions, paraformaldehyde in boiling 1,2-chloroethane with pivalic acid as catalyst, **29** was converted to a mixture of the oxadiazine **30** and the imidazoline oxide **33**, which were separated by chromatography. Both **30** and **33** yielded the imidazobenzodiazepine **31** upon refluxing in glacial acetic acid. The nitrone **33** was also converted to **31** by treatment with methoxide in methanol, most likely *via* the intermediate **34**.

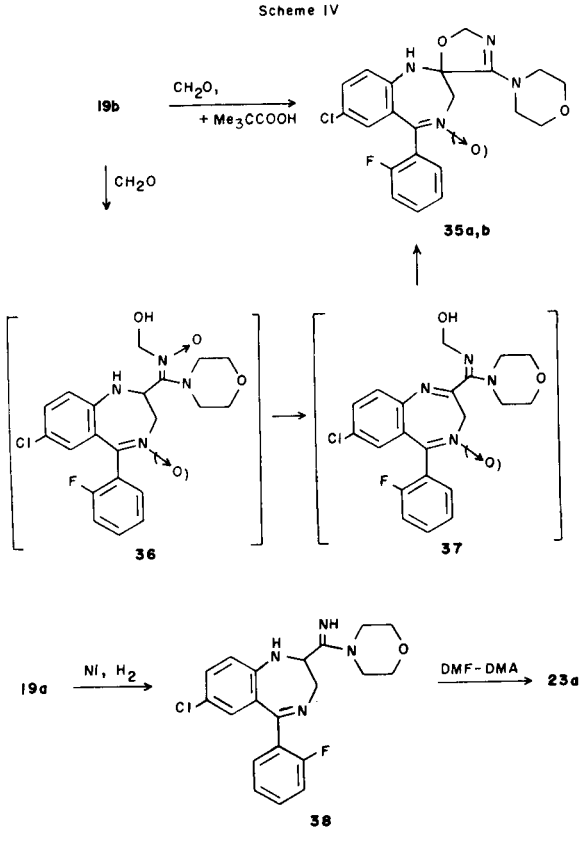
Compounds corresponding to the oxadiazine **30** and the imidazoline **33** were not isolated from the analogous reaction of the amidoxime **19b** with formaldehyde and pivalic acid in 1,2-dichloroethane. (Scheme IV). Instead, the spiro compound **35b**, the structure of which was determined by X-ray crystallographic analysis, was obtained. Phosphorus trichloride reduced **35b** to **35a**.

Scheme III



The formation of **35b** is thought to proceed by the intermediates **36** and **37**. Addition of formaldehyde to the oxime nitrogen would lead to the nitrone **36** which can rearrange and dehydrate to form **37**. Ring closure would finally give the spiro compound **35b**. *N*-Hydroxyamidines can be hydrogenated to amidines with Raney nickel as exemplified by the reduction of **19a** to **38**. Reaction of this amidine with dimethylformamide dimethylacetal provided another synthesis of the imidazobenzodiazepine **23a**.

Scheme IV



The nitrooximes have thus served as convenient starting materials for the preparation of a variety of new 2-substituted benzodiazepines and imidazo[1,5-*a*][1,4]benzodiazepines with a substitution pattern not easily accessible by other methods. The pharmacological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. The nmr spectra were recorded with a Varian T-60 instrument with TMS as internal standard. The ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

7-chloro-5-(2-fluorophenyl)-*N*-hydroxy-*alpha*-nitro-3*H*-1,4-benzodiazepine-2-methanimine (**2a**).

Sodium nitrite, 5 g (0.072 mole), was added in portions over a period of 5 minutes to a solution of 20 g (0.06 mole) of 7-chloro-5-(2-fluorophenyl)-2-nitromethylene-1,3-dihydro-2*H*-1,4-benzodiazepine **1a** (2) in 100 ml of glacial acid. Following the addition, the reaction mixture was stirred at room temperature for 15 minutes. The product, which crystallized partially during this period, was further precipitated by slow addition of 50 ml of water and collected by filtration. The crystals were washed with water, sucked dry and washed with methanol/ether to leave 13.5 g of light yellow product. The filtrate was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried and evaporated. Crystallization of the residue from methylene chloride/hexane yielded additional 3.5 g of product for a total yield of 17 g or 78%. The analytical sample was recrystallized from ether to give pale yellow crystals with mp 220-230° dec; uv: λ max 243 nm (ε 30,400) infl, 275 (13,700), 335 (5300); nmr (d-DMSO): δ 4.4 (s, 2, C_3-H), 7.0-8.0 (m, 7, aromatic H), 14.2 ppm (broad s, 1, OH).

Anal. Calcd. for $C_{16}H_{10}ClFN_4O_3$: C, 53.27; H, 2.79; N, 15.53. Found: C, 53.22; H, 2.80; N, 15.46.

7-Chloro-5-(2-fluorophenyl)-*N*-hydroxy-*alpha*-nitro-3*H*-1,4-benzodiazepine-2-methanimine 4-Oxide (**2b**).

7-Chloro-5-(2-fluorophenyl)-2-nitromethylene-2*H*-1,3-dihydro-1,4-benzodiazepine 4-oxide **1b** (3), 7 g (0.02 mole), was dissolved by heating in 250 ml of glacial acid. The solution was cooled with tap water and when the temperature reached 70° the addition of 1.9 g (0.0275 mole) of sodium nitrite was started. The sodium nitrite was added over a period of 10 minutes while cooling was continued. Following the addition, the mixture was stirred for ½ hour at room temperature, diluted with water and extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate yielded 6 g (79%) of yellow crystals. The analytical sample was recrystallized from methanol/ethyl acetate to give yellow crystals with undefined mp. The compound decomposes without prior melting; nmr (d-DMSO): δ 5.0 (s, 2, C_3-H), 6.9-8.0 (m, 7, aromatic H), *ca.* 14.5 ppm (broad s, 1, OH).

Anal. Calcd. for $C_{16}H_{10}ClFN_4O_4$: C, 51.01; H, 2.68; N, 14.87. Found: C, 51.32; H, 2.79; N, 14.69.

7-Chloro-5-(2-fluorophenyl)-*N*-methoxy-*alpha*-nitro-3*H*-1,4-benzodiazepine-2-methanimine (**3a**) and 7-Chloro-5-(2-fluorophenyl)-*N*-[(4-methoxy)-butoxy]-*alpha*-nitro-3*H*-1,4-benzodiazepine-2-methanimine (**11a**).

A solution of diazomethane in ether was added to a suspension of 6 g (0.0163 mole) of **2a** in 100 ml of tetrahydrofuran. After stirring at room temperature for 1 hour, the excess diazomethane was destroyed by addition of glacial acetic acid. The solvent was evaporated under reduced pressure and the residue was chromatographed over 100 g of silica gel using methylene chloride. Crystallization from ether/hexane gave 5.2 g (83%) of **3a** as light yellow crystals with mp 130-133°; uv: λ sh 215 nmr (ε 31,500) max 247 (30,000), sh 280 (15,500), sh 325 (5000), 347 (5500); ir (chloroform): 1560 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 4.15 (s, 3, OCH_3), 4.43 (s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{17}H_{12}ClFN_4O_3$: C, 54.58; H, 3.23; N, 14.95. Found: C, 54.49; H, 3.03; N, 14.76.

The more polar, minor by-product **11a** was crystallized from ether/hexane to yield 0.3 g (4%) of yellow crystals with mp 98-100°; uv: λ sh 212 nm (ε 25,100), max 247 (28,900), sh 275 (18,000), sh 327 (5600), max 346 (6200); ir (chloroform): 1616 cm^{-1} (C=N) 1560 (NO_2); nmr (deuteriochloroform) δ 1.75 [m, 4, $(CH_2)_2$], 3.30 (s, 3, OCH_3), 3.38 (t, J = 6 Hz, 2, OCH_2), 4.2-4.6 (m, 4, NCH_2 and C_4-H), 6.9-7.8 (m, 7, aromatic H): ms: m/e 445 (M^+).

Anal. Calcd. for $C_{21}H_{20}ClFN_4O_4$: C, 56.44; H, 4.51; N, 12.54. Found: C, 56.58; H, 4.64; N, 12.87.

7-Chloro-5-(2-fluorophenyl)-*N*-methoxy-*alpha*-nitro-3*H*-1,4-benzodiazepine-2-methanimine 4-Oxide (**3b**) and 7-Chloro-5-(2-fluorophenyl)-*N*-[(4-methoxy)butoxy]-*alpha*-nitro-3*H*-1,4-benzodiazepine-2-methanimine 4-Oxide (**11b**).

Reaction of 2.5 g (6.6 moles) of **2b** in 50 ml of tetrahydrofuran with etheral diazomethane gave similarly, after chromatography over 30 g of silica gel with 10% (v/v) of ethyl acetate in methylene chloride, 1.3 g

(50%) of **3b**, crystallized from ether as yellow crystals with mp 207-209°; nmr (deuteriochloroform): δ 4.25 (s, 3, OCH_3), 4.9 (s, 2, C_3-H), 6.9-7.6 (m, 7-aromatic H).

Anal. Calcd. for $C_{17}H_{12}ClFN_4O_4$: C, 52.25; H, 3.10; N, 14.34. Found: C, 52.51; H, 3.15; N, 14.04.

The more polar **11b** was crystallized from ether/hexane to yield 0.35 g (11.5%) of yellow crystals with mp 125-128°. The analytical sample was recrystallized from ether; nmr (deuteriochloroform): δ 1.73 (m, 4, CH_2CH_2), 3.34 (s, 3, OCH_3), 3.36 (t, J = 6 Hz, OCH_2), 4.43 (t, J = 6 Hz, $N-CH_2$), 4.86 (s, 2, C_3-H), 7.0-7.7 (m, 7, aromatic H).

Anal. Calcd. for $C_{21}H_{20}ClFN_4O_5$: C, 54.49; H, 4.36; N, 12.10. Found: C, 54.20; H, 4.51; N, 11.89.

An 80% yield of **3** obtained without the formation of **11b** if the reaction with diazomethane was carried out in methylene chloride instead of tetrahydrofuran.

7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-*N'*-hydroxycarboximidamide (**4a**).

A mixture of 7.2 g (0.02 mole) of **2a** and 50 ml of ethanol containing 20% (v/v) of ammonia was allowed to sit at room temperature overnight. The precipitated crystals were collected, washed with methanol, 2-propanol and ether to leave 4.6 g (69%) of product. The analytical sample was recrystallized from tetrahydrofuran/ethanol to give yellowish crystals with mp 248-249° dec; uv: λ max 224 nm (ε 31,600), 310 (12,400); nmr (d-DMSO): δ 4.33 (broad s, 2, C_3-H), 5.7 (s, 2, NH_2), 7-7.8 (m, 7, aromatic H), 10.7 (s, 1, OH).

Anal. Calcd. for $C_{16}H_{12}ClFN_4O$: C, 58.10; H, 3.66; N, 16.94. Found: C, 58.05; H, 3.37; N, 16.74.

7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-*N'*-hydroxycarboximidamide 4-Oxide (**4b**).

A mixture of 1 g (2.65 mmoles) of **2b** and 20 ml of methanol containing 20% (v/v) of ammonia was allowed to sit overnight. The precipitated crystals were collected, washed with methanol, water and methanol to yield 0.8 g (87%) of product with mp 252-254° dec. For analysis it was recrystallized from methanol/ethanol/tetrahydrofuran to give yellow crystals with mp 258-260° dec.

Anal. Calcd. for $C_{16}H_{12}ClFN_4O_2$: C, 55.42; H, 3.49; N, 16.16. Found: C, 55.42; H, 3.52; N, 16.02.

7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-*N'*-hydroxy-*N*-methylcarboximidamide (**5a**).

A solution of 3.6 g (0.01 mole) of **2a** in 50 ml of ethanol containing 20% (v/v) of methylamine was allowed to stand at room temperature overnight. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and water. The organic phase was dried and evaporated and the residue was crystallized from ether to give 2.1 g (61%) of yellowish crystals. The analytical sample was recrystallized from methylene chloride/ethyl acetate/hexane, mp 223-225° dec; uv: λ max 226 nm (ε 32,200), 319 (9400); nmr (deuteriochloroform + d_6-DMSO): δ 3.12 (d, 3, J = 5 Hz, $-CH_3$), 4.4 (broad s, 2, C_3-H), 5.38 (q, 1, J = 5 Hz, NH), 6.8-7.8 (m, 7, aromatic H), 10.2 (s, 1, OH).

Anal. Calcd. for $C_{17}H_{14}ClFN_4O$: C, 59.22; H, 4.09; N, 16.25. Found: C, 59.41; H, 4.10; N, 16.12.

7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-*N'*-hydroxy-*N,N*-dimethylcarboximidamide (**6a**).

Reaction of **2a**, 7.2 g (0.02 mole), with dimethylamine in tetrahydrofuran yielded similarly 4.5 g (62%) of product which was recrystallized from methanol/ethyl acetate for analysis, mp 160-164°; uv: λ max 221 nm (ε 37,800), 320 (7300); nmr (deuteriochloroform + d-DMSO): δ 2.87 (s, 6, CH_3), 4.3 (broad s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H), 10.5 (s, 1, OH).

Anal. Calcd. for $C_{18}H_{16}ClFN_4O$: C, 60.26; H, 4.49; N, 15.62. Found: C, 60.44; H, 4.53; N, 15.88.

7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-*N'*-hydroxy-*N,N*-dimethylcarboximidamide 4-Oxide (**6b**).

In a similar manner, **6b** was prepared in 80% yield by reaction of **2b** with dimethylamine in tetrahydrofuran. Crystallization from ethyl acetate and recrystallization from methanol/ethyl acetate gave yellow crystals with mp 190-192° dec; nmr (deuteriochloroform): δ 2.9 (s, 6, CH_3), 4.8 (broad s, 2, C_3-H), 6.8-7.6 (m, 7, aromatic H), 10.8 (s, 1, OH).

Anal. Calcd. for $C_{18}H_{16}ClFN_4O_2$: C, 57.68; H, 4.30; N, 14.95. Found: C, 57.85; H, 4.18; N, 14.76.

7-Chloro-5-(2-fluorophenyl)-2-[4-[(hydroxyimino)methyl]morpholinyl]-3*H*-1,4-benzodiazepine (**7a**).

Morpholine, 5 ml, was added to a suspension of 5 g of **2a** in 75 ml of tetrahydrofuran. After standing at room temperature for 6 hours, the reaction mixture was filtered and the filtrate was evaporated. The residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ether to yield 4.8 g (86%) of yellow crystals. The analytical sample was recrystallized from methanol/ethyl acetate, mp 191-193° dec.

Anal. Calcd. for $C_{20}H_{18}ClFN_4O$: C, 59.93; H, 4.53; N, 13.98. Found: C, 59.84; H, 4.44; N, 13.75.

7-Chloro-5-(2-fluorophenyl)-2-[4-[(hydroxyimino)methyl]morpholinyl]-3*H*-1,4-benzodiazepine 4-Oxide (**7b**).

Reaction of **2b** with solution of morpholine in tetrahydrofuran gave similarly **8b** in 86% yield. It was crystallized from ethyl acetate and recrystallized from analysis from a mixture of methanol/tetrahydrofuran/ethyl acetate to give yellow crystals with mp 211-213° dec.

Anal. Calcd. for $C_{20}H_{18}ClFN_4O_3$: C, 57.63; H, 4.35; N, 13.44. Found: C, 57.71; H, 4.26; N, 13.48.

7-Chloro-5-(2-fluorophenyl)-*N'*-methoxy-3*H*-1,4-benzodiazepine-2-carboximidamide (**8a**).

A mixture of 1.5 g (0.004 mole) of **3a** and 20 ml of methanol containing 20% (v/v) of ammonia was allowed to stand at room temperature for 4½ hours. After partial evaporation, the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride layer was dried and evaporated. The residue was passed over neutral alumina using ether. Crystallization of the combined eluates from ether/hexane gave 0.9 g (65%) of colorless crystals with mp 120-124°; nmr (deuteriochloroform): δ 4.0 (s, 3, OCH_3), 4.45 (broad s, 2, C_3-H), 5.2 (broad s, 2, NH_2), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{17}H_{14}ClFN_4O$; C, 59.22; H, 4.09; N, 16.25. Found: C, 59.25; H, 3.84; N, 16.25.

7-Chloro-5-(2-fluorophenyl)-*N*-methoxy-3*H*-1,4-benzodiazepine-2-carboximidic Acid Methyl Ester (**9a**).

Compound **3a**, 4 g (10.7 mmole) was added to a solution of 4 g of potassium *t*-butoxide in 100 ml of methanol. After stirring at room temperature for 1 hour, the bulk of the solvent was evaporated under reduced pressure and the remainder was partitioned between methylene chloride and aqueous sodium bicarbonate. The organic phase was dried and evaporated. Crystallization of the residue from ether/methylene chloride/hexane yielded 3.1 g (80%) of crystals with mp 164-165°. For analysis, it was recrystallized from ethyl acetate/hexane, mp 165-166°; nmr (deuteriochloroform): δ 3.97 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), 4.4 (broad s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{18}H_{15}ClFN_3O_2$: C, 60.09; H, 4.20; N, 11.68. Found: C, 60.01; H, 4.12; N, 11.59.

7-Chloro-5-(2-fluorophenyl)-*N*-methoxy-3H-1,4-benzodiazepine-2-carboximidic Acid Methyl Ester 4-Oxide (**9b**).

Compound **3b**, 7.8 g (0.02 mole) was added to a solution of 5 g of potassium *t*-butoxide in 200 ml of methanol. After stirring for 1 hour at room temperature, the methanol was partially evaporated under reduced

pressure and the residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from methanol gave 5.8 g (77%) of product containing methanol. The analytical sample crystallized from ether with 0.5 mole solvent to give light yellow crystals with mp 80-82°; nmr (deuteriochloroform): δ 4.0 (s, 3, OCH_3), 4.1 (s, 3, OCH_3), 4.85 (broad s, 2, C_3-H), 6.9-7.7 (m, 7, aromatic H).

Anal. Calcd. for $C_{18}H_{15}ClFN_3O_3 \cdot 0.5\ Et_2O$: C, 58.19; H, 4.88; N, 10.18. Found: C, 58.19; H, 4.84; N, 10.25.

7-Chloro-5-(2-fluorophenyl)-*N*-hydroxy-3*H*-1,4-benzodiazepine-2-carboximidothioic Acid Methyl Ester 4-Oxide (**10b**).

A suspension of 5 g of potassium *t*-butoxide in 200 ml of tetrahydrofuran was saturated with methanthiol and 3.78 g (0.01 mole) of **2b** was added. The mixture was stirred for 1 hour at room temperature, then neutralized by addition of acetic acid and partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized from tetrahydrofuran/ethyl acetate to yield 2 g (52.5%) of light yellow product with mp 220-222° dec; nmr (DMSO): δ 2.56 (s, 3, SCH_3), 4.96 (broad s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H), 13.05 (s, 1, OH).

Anal. Calcd. for $C_{17}H_{13}ClFN_3O_2S$: C, 54.04; H, 3.47; N, 11.12. Found: C, 54.34; H, 3.38; N, 10.88.

7-Chloro-5-(2-fluorophenyl)-2-methoxy-3*H*-1,4-benzodiazepine 4-Oxide (**13**).

Compound **2b**, 0.5 g (1.32 mmoles) was added to a solution of 0.5 g of potassium *t*-butoxide in 10 ml of methanol. After stirring at room temperature for 1 hour, the mixture was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was crystallized from ether to yield 0.35 g (82.5%) of yellow crystals with mp 188-190°. The analytical sample was recrystallized from ether/hexane, mp 192-195°; δ 3.96 (s, 3, OCH_3), 4.56 (s, 2, CH_2), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{16}H_{12}ClFN_2O_2$: C, 60.29; H, 3.80; N, 8.79. Found: C, 60.30; H, 3.72; N, 8.80.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2(2*H*)-one (**15**).

Aqueous sodium hydroxide solution, 5 ml of 1*N*, was added to a warm solution of 0.3 g (0.8 mmoles) of **3a** in 20 ml of 2-propanol. After standing for 1 hour at ambient temperature, the mixture was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether gave 150 mg (65%) of **15** with mp 203-206°, identical with an authentic sample (6).

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine-2-*N'*-hydroxycarboximidamide (**16a**).

Compound **4a**, 5 g (0.015 mole) was dissolved by warming in a mixture of 250 ml of ethanol and 100 ml of tetrahydrofuran. Sodium borohydride, 2 g (0.053 mole) was added at room temperature and the mixture was stirred overnight. The solvents were evaporated partially under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ethyl acetate to yield 3.4 g (65%) of yellowish product. The analytical sample was recrystallized from ethyl acetate/hexane, mp 216-218°; nmr (d-DMSO): δ 3.6-4.4 (m, 3, C_2-H, C_3-H), 5.44 (broad s, 2, NH_2), 6.4 (d, 1, J = 2 Hz, NH), 6.67 (d, 1, J = 2 Hz, C_6-H), 6.91 (d, 1, J = 8.5 Hz, $C_{10}-H$), 7-7.6 (m, 5, aromatic H), 9.22 (s, 1, OH).

Anal. Calcd. for $C_{16}H_{14}ClFN_4O$: C, 57.75; H, 4.24; N, 16.84. Found: C, 57.75; H, 4.20; N, 16.63.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine-2-*N'*-hydroxy-*N*-methylcarboximidamide (**17a**).

Reduction of 3.45 g (0.01 mole) of **5a** with 1 g (0.026 mole) of sodium borohydride in 100 ml of ethanol for 4 hours at room temperature gave after the workup described above, 2.55 g (74%) of product, crystallized from ethyl acetate. The analytical sample was recrystallized from methanol/ethyl acetate, mp 215-217° dec; uv: λ sh 223 nm (ε 32,600), sh 266 (9100), max 368 (3700): nmr (d-DMSO): δ 2.8 (d, 3, J = 5 Hz, $NHCH_3$), 3.66 (q, 1, J_{AB} = 11.5 Hz, J_{AX} = 8 Hz, C_3-H), 4.1-4.5 (m, 2, C_3-H and C_2-H), 5.66 (q, 1, J = 5 Hz, NH), 6.45 (broad s, 1, NH), 6.6-7.6 (m, 7, aromatic H), 9.35 (s, 1, OH).

Anal. Calcd. for $C_{17}H_{16}ClFN_4O$: C, 58.88; H, 4.65; N, 16.16. Found: C, 58.74; H, 4.60; N, 16.11.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine-2-*N'*-hydroxy-*N,N*-dimethylcarboximidamide (**18a**).

This compound was similarly obtained by treatment of **6a** in ethanol/tetrahydrofuran with sodium borohydride for 4 hours at room temperature. The usual workup and crystallization from ether gave 58% of product. For analysis it was recrystallized from methanol/ethyl acetate, mp 178-180°.

Anal. Calcd. for $C_{18}H_{18}ClFN_4O$: C, 59.92; H, 5.03; N, 15.53. Found: C, 60.03; H, 5.04; N, 15.21.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiaxepine-2-(*N'*-hydroxy-*N,N*-dimethylcarboximidamide (**18b**).

Reduction of **6b** with sodium borohydride in ethanol for 3 hours at room temperature gave this compound in 66% yield . For analysis it was recrystallized from ethyl acetate/ether, mp 145-150° dec (solvate with 1/6 mole of ether).

Anal. Calcd. for $C_{18}H_{18}ClFN_4O_2 \cdot 1/6(C_2H_5)_2O$: C, 57.61; H, 5.09; N, 14.39. Found: C, 57.50; H, 5.28; N, 14.57.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*N*-hydroxy-*alpha*-(4-morpholinyl)-1*H*-1,4-benzodiazepine-2-methanimine (**19a**).

This compound was obtained in 74% yield by reduction of **7a** with sodium borohydride in ethanol/tetrahydrofuran (4 hours at room temperature). It was crystallized from ether and recrystallized from methanol/ethyl acetate/hexane for analysis to give off white needles with mp 133-137°.

Anal. Calcd. for $C_{20}H_{20}ClFN_4O_2$: C, 59.63; H, 5.00; N, 13.91. Found: C, 59.68; H, 5.04; N, 14.09.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*N*-hydroxy-*alpha*-(4-morpholinyl)-1*H*-1,4-benzodiazepine-2-methanimine 4-Oxide (**19b**).

Analogously, reduction of **7b** gave this compound in 75% yield. It was crystallized from ethyl acetate and recrystallized from methanol/ethyl acetate for analysis to leave light yellow crystals with mp 192-193° dec.

Anal. Calcd. for $C_{20}H_{20}ClFN_4O_3$: C, 57.35; H, 4.81; N, 13.38. Found: C, 57.58; H, 4.92; N, 13.24.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*N*-hydroxy-1*H*-1,4-benzodiazepine-2-carboximidothioic Acid Methyl Ester 4-Oxide (**21b**).

A mixture of 2 g (5.3 mmoles) of **10b**, 1 g of sodium borohydride, 100 ml of ethanol and 50 ml of tetrahydrofuran was stirred at room temperature for 2 hours. The reaction mixture was evaporated partially under reduced pressure and the residue was partitioned between methylene chloride (large volume) and aqueous sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized with ethanol and collected with ether to give 1.8 g (90%) of yellow crystals. The analytical sample was recrystallized from methanol/ethyl acetate, mp 215-217° dec.

Anal. Calcd. for $C_{17}H_{15}ClFN_3O_2S$: C, 53.76; H, 3.98; N, 11.06. Found: C, 53.80; H, 3.80; N, 11.04.

8-Chloro-3-dimethylamino-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (**22a**).

A mixture of 1.8 g (5 mmoles) of **18a**, 0.5 g (16.6 mmoles) of paraformaldehyde, 0.1 g of *p*-toluenesulfonic acid hydrate and 100 ml of ethanol was heated to reflux for 5 hours. The solvent was evaporated under

reduced pressure and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization from ether/2-propanol gave 0.8 g (46%) of product which was purfied by chromatography over 30 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The analytical sample was recrystallized from ethyl acetate/hexane to give light yellow crystals with mp 161-162°; uv: λ max 217 nm (ε 46,400), sh 244 (20,000), sh 272 (6800); nmr (deuteriochloroform): δ 2.88 [s, 6, $N(CH_3)_2$], 4.76 (broad s, 2, C_4-H), 6.8-7.8 (m, 8, aromatic H, C_1-H).

Anal. Calcd. for $C_{19}H_{16}ClFN_4$: C, 64.32; H, 4.55; N, 15.78. Found: C, 64.44; H, 4.71; N, 15.62.

The dihydrochloride of this compound was prepared by treating a solution in ethanol with excess ethanolic hydrogen chloride and crystallizing by addition of ether. The analytical sample was recrystallized from ethanol/ether and had mp 178-182° dec.

Anal. Calcd. for $C_{19}H_{16}ClFN_4 \cdot 2HCl$: C, 53.35; H, 4.24; N, 13.10; Cl, 24.87. Found: C, 53.61; H, 4.22; N, 12.99; Cl, 24.80.

8-Chloro-3-dimethylamino-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine 5-Oxide (**22b**).

A mixture of 3.8 g (0.01 mole) of **18b**, 1 g (0.033 mole) of paraformaldehyde, 0.3 g of *p*-toluenesulfonic acid hydrate and 150 ml of ethanol was heated to reflux for 20 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from ether/2-propanol gave 1.1 g (30%) of yellow crystals. The analytical sample was purified by chromatography over silica gel using 5% (v/v) of ethanol in methylene chloride and crystallized from ethyl acetate/hexane to give yellow crystals with mp 203-206°; uv: λ max 226 nm (ε 33,300), sh 253 (19,000), 298 (16,500), sh 390/410 (600); nmr (deuteriochloroform): δ 2.96 [s, 6, $N(CH_3)_2$], 5.2 (center of degenerated AB-system, 2, C_4-H), 6.9-7.5 (m, 7, aromatic H), 7.65 (s, 1, C_1-H).

Anal. Calcd. for $C_{19}H_{16}ClFN_4O$: C, 61.54; H, 4.35; N, 15.11. Found: C, 61.67; H, 4.44; N, 15.19.

8-Chloro-6-(2-fluorophenyl)-3-(morpholinyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (**23a**).

A solution of 0.15 g of (0.39 mmole) of **38**, 0.5 ml of dimethyl formamide and 10 ml of toluene was heated to reflux for 5 hours. After evaporation under reduced pressure, the residue was chromatographed over 5 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The fractions containing product were combined and evaporated and the residue was crystallized from ether to yield 70 mg (45%) of light yellow crystals with mp 177-179°; nmr (deuteriochloroform): δ 3.16 [m, 4, $N(CH_2)_2$], 3.84 [m, 4, $O(CH_2)_2$], 4.67 (broad s, 2, C_4-H), 6.8-7.7 (m, 7, aromatic H), 7.7 (s, 1, C_1-H).

Anal. Calcd. for $C_{21}H_{18}ClFN_4O$: C, 63.56; H, 4.57; N, 14.12. Found: C, 63.73; H, 4.54; N, 14.41.

8-Chloro-6-(2-fluorophenyl)-3-morpholino-4*H*-imidazol[1,5-*a*][1,4]benzodiazepine 5-Oxide (**23b**).

A mixture of 3 g (7.1 mmoles) of **19b**, 0.6 g (20 mmoles) of paraformaldehyde, 100 ml of ethanol and 250 mg of *p*-toluenesulfonic acid hydrate was heated to reflux for 16 hours. The crude product obtained after the usual workup was chromatographed over 60 g of silica gel using 5% (v/v) of ethanol in methylene chloride for elution. The clean fractions of product were combined and evaporated. The residue was crystallized from ether and recrystallized from ethyl acetate/hexane for analysis to yield 0.53 g (18%) of yellow crystals with mp 200-203°; nmr (deuteriochloroform): 3.33 [m, 4, $N(CH_2)_2$], 3.85 [m, 4, $O(CH_2)_2$], 5.2 [d, (degenerate AB-system), 2, C_4-H), 7-7.7 (m, 7, aromatic H), 7.8 (s, 1, C_1-H).

Anal. Calcd. for $C_{21}H_{18}ClFN_4O_2$: C, 61.09; H, 4.39; N, 13.57. Found: C, 61.07; H, 4.40; N, 13.31.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-morpholino-4*H*-imidazo[1,5-*a*]-[1,4]benzodiazepine (**24a**).

A mixture of 1 g of **24b**, 25 ml of tetrahydrofuran, 25 ml of ethanol, and *ca.* 5 g of Raney nickel (type 28) was stirred under an atmosphere of hydrogen for 15 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was passed over a pad of silica gel using 5% (v/v) of ethanol in methylene chloride for elution. The eluates were evaporated and crystallized from ether/hexane to give 0.5 g (52%) of light yellow crystals with mp 173-175°. The analytical sample was recrystallized from ethyl acetate/hexane, mp 175-177°.

Anal. Calcd. for $C_{22}H_{20}ClFN_4O$: C, 64.31; H, 4.91; N, 13.64. Found: C, 64.33; H, 4.91; N, 13.56.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-morpholino-4*H*-imidazo[1,5-*a*]-[1,4]benzodiazepine 5-Oxide (**24b**).

A mixture of 4.2 g (0.01 mole) of **19b**, 50 ml of glacial acetic acid and 4 ml of acetaldehyde was heated to reflux for 5 minutes. The cooled reaction mixture was poured on ice, made alkaline with ammonia and extracted with methylene chloride. The extracts were dried and evaporated and the residue was crystallized from ether/2-propanol to yield 2.7 g (63%) of yellow crystals. For analysis, the product was purified by passing over silica gel using 5% (v/v) of ethanol in methylene chloride and crystallized from ethyl acetate, mp 217-220° dec; nmr (deuteriochloroform): δ 2.52 (s, 3, CH_3), 3.28 [m, 4, $N(CH_2)_2$], 3.52 [m, 4, $O(CH_2)_2$], 4.95 (d, 1), and 5.3 (d, 1) (AB-system, J = 14 Hz, C_4-H), 6.9-7.7 (m, 7, aromatic H).

Anal. Calcd. for $C_{22}H_{20}ClFN_4O_2$: C, 61.90; H, 4.72; N, 13.13. Found: C, 61.99; H, 4.51; N, 12.99.

8-Chloro-6-(2-fluorophenyl)-3-methoxy-1-methyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (**25a**).

A mixture of 3 g (8.3 mmoles) of **9a**, 100 ml of ethanol, 50 ml of tetrahydrofuran and 1.5 g of sodium borohydride was stirred at room temperature for 8 hours and was kept in the refrigerator over night. The solvents were partially evaporated under reduced pressure and the remainder was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was chromatographed over 60 g of silica gel using methylene chloride/ethyl acetate, 1:1 (v/v). After elution of an orange byproduct and some mixed fractions, 1.4 g (46%) of clean 7-chloro-5-(2-fluorophenyl)-2,3-dihydro-*N*-methoxy-1*H*-1,4-benzodiazepine-2-carboximidoic acid methyl ester (**20a**) was obtained as a yellowish resin. This material was dissolved in 25 ml of glacial acetic acid. The solution was treated with 1 ml of acetaldehyde and the mixture was heated on the steam bath for 15 minutes. After evaporation, the residue was partitioned between methylene chloride and aqueous ammonia and the organic phase was dried and evaporated. The residue was chromatographed over 50 g of silica gel using methylene chloride/ethyl acetate, 1:1 (v/v) for elution. The fractions containing clean product were combined and evaporated and crystallized from ether/hexane to give 0.2 g (14.5%) of yellowish crystals with mp 154-155°. The analytical sample was recrystallized from ethyl acetate/hexane; nmr (deuteriochloroform): δ 2.5 (s, 3, CH_3), 3.93 (s, 3, OCH_3), 3.96 (d, 1) and 5.22 (d, 1) (AB-system, J = 13 Hz, C_4-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{15}ClFN_3O$: C, 64.14; H, 4.25; N, 11.81. Found: C, 64.19; H, 4.26; N, 11.80.

8-Chloro-6-(2-fluorophenyl)-3-methoxy-1-methyl-4*H*-imidazo[1,5-*a*]-[1,4]benzodiazepine 5-Oxide (**25b**).

A mixture of 3 g (7.3 mmoles) of **9b**, 100 ml of ethanol, 50 ml of tetrahydrofuran and 1.5 g of sodium borohydride was stirred at room temperature for 4 hours. The reaction mixture was partially evaporated under reduced pressure and the remainder was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated and the residue of crude 7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*N*-methoxy-1*H*-1,4-benzodiazepine-2-carboximidic acid methyl ester 4-oxide (**20b**) was dissolved in 50 ml of glacial acetic acid. The solution was treated with 2 ml of acetaldehyde and heated on the steam bath for 15 minutes. After evaporation, the residue was parti-

tioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was chromatographed over 50 g of silica gel using 25% (v/v) of methylene chloride in ethyl acetate. Crystallization of the combined evaporated fractions from ethyl acetate/ether yielded 1.5 g (55%) of colorless crystals. The analytical sample was recrystallized from ethyl acetate/hexane, mp 189-200° dec; nmr (deuteriochloroform): δ 2.5 (s, 3, CH_3), 3.97 (s, 3, OCH_3), 4.9 (d, 1) and 5.2 (d, 1) (AB-system, J = 14 Hz), C_4-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{15}ClFN_3O_2$: C, 61.38; H, 4.07; N, 11.30. Found: C, 61.40; H, 4.08; N, 11.30.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-(methylthio)-4H-imidazo[1,5-*a*][1,4]benzodiazepine (**26a**).

Phosphorus trichloride, 2 ml, was added to a solution of 0.5 g (1.29 mmoles) of **26b** in 10 ml of methylene chloride. The mixture was allowed to stand at room temperature for 4 hours and in the refrigerator over the weekend. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% sodium carbonate solution. The organic phase was dried and evaporated and the residue was chromatographed over 15 g of silica gel using methylene chloride/ethyl acetate, 1:1 (v/v) for elution. The clean fractions were combined and evaporated and the residue was crystallized from ethyl acetate/hexane to leave 0.33 g (69%) of colorless crystals with mp 188-190°; nmr (deuteriochloroform): δ 2.43 (s, 3, CH_3), 2.57 (s, 3, SCH_3), 3.95 (d, 1), and 5.36 (d, 1) (AB-system, J = 13 Hz, C_4-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{15}ClFN_3S$: C, 61.37; H, 4.07; N, 11.30. Found: C, 61.27; H, 3.92; N, 11.51.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-(methylthio)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 5-Oxide (**26b**).

Acetaldehyde, 1.5 ml, was added to a suspension of 1.52 g (3 mmoles) of **21b** in 30 ml of glacial acetic acid. The mixture was heated on the steam bath for 1 hour. After evaporation under reduced pressure, the residue was partitioned between methylene chloride and aqueous ammonia. The organic layer was separated, dried and filtered over a pad of silica gel using ethyl acetate for elution. The eluate was evaporated and the residue was crystallized from ethyl acetate/ether to give 0.85 g (73%) of product. The analytical sample was recrystallized from ethyl acetate/hexane, mp 205-207°; nmr (deuteriochloroform): δ 2.46 (s, 3, CH_3), 2.60 (s, 3, SCH_3), 4.93 (d, 1) and 5.36 (d, 1) (AB-system, J = 14 Hz, C_4-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{15}ClFN_3OS$: C, 58.84; H, 3.90; N, 10.83. Found: C, 58.78; H, 3.76; N, 11.01.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-(methylsulfonyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine (**27a**).

A mixture of 0.35 g (0.83 mmole) of **27b**, 2 ml of phosphorus trichloride and 25 ml of methylene chloride was allowed to sit at room temperature for 2 days. After evaporation under reduced pressure the residue was partitioned between methylene chloride and sodium carbonate solution. The organic layer was dried and evaporated and the residue was crystallized from ethyl acetate/hexane to give 0.3 g (89%) of colorless crystals. The analytical sample was recrystallized from the same solvents, mp 224-245°; nmr (deuteriochloroform): δ 2.57 (s, 3, CH_3), 3.16 (s, 3, SO_2CH_3), 3.92 (d, 1) and 5.93 (d, 1) (AB-system, J = 13 Hz, C_4-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{15}ClFN_3O_2S$: C, 56.51; H, 3.74; N, 10.40. Found: C, 56.59; H, 3.85; N, 10.39.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-(methylsulfonyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine 5-Oxide (**27b**).

A solution of 0.45 g (1.16 mmoles) of **26b** in 30 ml of methylene chloride was treated with 1.5 g (8.7 mmoles) of *m*-chloroperbenzoic acid. After stirring at room temperature for 1 hour, the solution was washed with 10% aqueous sodium carbonate solution, dried and evaporated. The residue was crystallized from ethyl acetate to yield 0.42 g (86%) of colorless product. For analysis, it was recrystallized from methanol/ethyl acetate, mp 240-241° dec; nmr (deuteriochloroform) δ 2.62 (s, 3, CH_3), 3.2 (s, 3, SO_2CH_3), 4.95 (d, 1) and 5.88 (d, 1) (AB-spectrum, J = 14 Hz, C_4-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{19}H_{15}ClFN_3O_3S$: C, 54.35; H, 3.69; N, 10.01. Found: C, 54.27; H, 3.42; N, 10.10.

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine-2-carboxaldoxime (**29**) (2).

Sodium borohydride, 1.6 g (0.042 mole) was added in two portions at 15 minute intervals to a suspension of 3.6 g (0.01 mole) of **2a** in 50 ml of ethanol. After stirring for 4 hours at room temperature the reaction mixture was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether yielded 1.7 g (53%) of yellowish crystals with mp 185-190°. Recrystallization from methylene chloride/ethyl acetate raised the mp to 193-195°.

9-Chloro-7-(2-fluorophenyl)-4a,5-dihydro-1*H*-[1,2,5]oxadiazino[5,4-*a*][1,4]benzodiazepine (**30**) and 8-Chloro-6-(2-fluorophenyl)-3a,4-dihydro-1*H*-imidazo[1,5-*a*][1,4]benzodiazepine 2-Oxide (**33**).

A mixture of 3.2 g (0.01 mole) of **29**, 1.0 g of paraformaldehyde, 1.0 g of pivalic acid and 150 ml of 1,2-dichloroethane was heated to reflux for 30 minutes with separation of water. The reaction mixture was washed with saturated sodium bicarbonate solution, dried and evaporated. The residue was chromatographed over 60 g of silica gel using 5% (v/v) of ethanol in methylene chloride followed by 10% ethanol in methylene chloride. The fractions containing the less polar oxadiazine were combined and evaporated. Crystallization from ether yielded 0.8 g (24%) of product **30** which was recrystallized from ethyl acetate/methanol for analysis to give colorless needles with mp 230-233°; nmr (deuteriochloroform) ($CDCl_3$ + 5% d-DMSO): δ 3.40 (q, 1, J_{AB} = 11 Hz, J_{AX} = 12 Hz, C_5-H), 4.18 (q, 1, J_{AB} = 11Hz, J_{BX} = 3.5 Hz, C_5-H), 5.0 (q with fine structure, 1, J_{AX} = 12 Hz, J_{BX} = 3.5 Hz, $C_{4a}-H$), 5.36 (center of AB-system, 2, J = 12 Hz, C_1-H), 6.8-7.8 (m, 8, aromatic H and C_4-H).

Anal. Calcd. for $C_{17}H_{13}ClFN_3O$: C, 61.92; H, 3.97; N, 12.74. Found: C, 61.84; H, 4.00; N, 12.70.

The fractions containing the more polar component were combined and evaporated and the residue was crystallized from ether to yield 550 mg (16.5%) of the *N*-oxide **33** with mp 182-184°; nmr (deuteriochloroform): δ 3.66 (q, 1, J_{AB} = 12.5 Hz, J_{AX} = 7 Hz, C_4-H), 4.65 (d, 1, J_{AB} = 12.5 Hz, C_4-H), 4.8 (m, 1, $C_{3a}-H$), 5.32 (center of AB-system with fine structure, 2, C_1-H), 6.46 (d, 1, J = 8.5 Hz, $C_{10}-H$), 6.8-7.8 (m, 7, aromatic H, C_3-H).

Anal. Calcd. for $C_{17}H_{13}ClFN_3O$: C, 61.92; H, 3.97; N, 12.74. Found: C, 61.75; H, 3.92; N, 12.60.

8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (**31**).

A) A mixture of 0.2 g (0.64 mmole) of **29**, 0.1 g (3.3 mmoles) of paraformaldehyde and 5 ml of glacial acetic acid was heated to reflux for 5 minutes. The reaction mixture was worked up as described in the previous example and the crude product was chromatographed over 5 g of silica gel using 5% (v/v) of ethanol in methylene chloride. Crystallization of the combined fractions from ether/hexane gave 70 mg of tan crystals. Recrystallization from ethyl acetate/hexane gave 70 mg (35%) of product with mp 150-151°; nmr (deuteriochloroform): δ 4.65 (broad s, 2, C_4-H), 6.8-7.8 (m, 8, aromatic H), 7.95 (s, 1, C_1-H).

Anal. Calcd. for $C_{17}H_{11}ClFN_3$: C, 65.60; H, 3.56; N, 13.48. Found: C, 65.59; H, 3.71; N, 13.40.

B) A solution of 0.15 g of **30** in 5 ml of glacial acetic acid was heated to reflux for 15 minutes. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated. Chromatography of the residue on 5 g of silica gel using 5% (v/v) of ethanol in methylene chloride and crystallization from ether containing a few drops of 2-propanol yielded 0.08 g (56.5%) of product with mp 148-151°.

C) A solution of 50 mg of **33** in 3 ml of glacial acetic acid was heated to reflux for 15 minutes. The mixture was worked up as described above and the product was isolated by chromatography over 3 g of silica gel using 5% (v/v) ethanol in methylene chloride. Crystallization from ether yielded 28 mg (59%) of product with mp 149-151°.

D) A solution of 50 mg of **33** in 3 ml of methanol containing 25 mg of potassium *t*-butoxide was heated to reflux for 10 minutes. The mixture was evaporated partially and the residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether yielded 30 mg (63.5%) of product with mp 148-151°.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (**32**) (2).

A mixture of 0.32 g (1 mmole) of **29**, 15 ml of glacial acetic acid and 0.3 ml of acetaldehyde was heated to reflux for 10 minutes. The acetic acid was evaporated under reduced pressure and the residue was partitioned between methylene chloride and dilute aqueous ammonia. The organic phase was dried and evaporated and the brown residue was chromatographed over 7 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The fractions containing product were combined and evaporated. The base was dissolved in 2-propanol and the solution was treated with 0.11 g (0.95 mmole) of maleic acid. The maleate was crystallized by addition of ether. The tan crystals were collected and dried at 90° under vacuum to yield 0.265 g (60%) with mp 148-151°. Liberation of the base and crystallization from ether gave colorless crystals with mp 158-160°, identical with the previously prepared material (2).

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-4'-(4-morpholinyl)spiro[2*H*-1,4-benzodiazepine-2,5'-[2*H*](5*H*)-oxazole] (**35a**).

A mixture of 1.3 g (3 mmoles) of **35b**, 50 ml of methylene chloride and 2.6 ml of phosphorus trichloride was allowed to sit at room temperature for 4 hours and was washed with aqueous sodium bicarbonate and dilute ammonia. The organic phase was dried and evaporated and the residue was chromatographed over 25 g of silica gel using methylene chloride/-ethyl acetate 1:3 (v/v) followed by 3% (v/v) of ethanol in methylene chloride. First was eluted 0.37 g (31%) of **23a** with mp 177-179°. Then, 0.22 g (18%) of **35a** was crystallized from ether, mp 162-165°; nmr (deuteriochloroform): δ 3.48 (s, 8, morpholine), 3.66 (d, 1) and 4.22 (d, 1) (AB-system, J = 12 Hz, C_3-H), 4.5 (s, 1, NH), 5.28 (AB-system, J = 8.5 Hz, C_2-H), 6.8 (d, 1, J = 8 Hz, C_9-H), 7.0-7.8 (m, 6, aromatic H).

Anal. Calcd. for $C_{21}H_{20}ClFN_4O_2$: C, 60.80; H, 4.86; N, 13.51. Found: C, 60.68; H, 4.80; N, 13.52.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-4'-(4-morpholinyl)spiro[2*H*-1,4-benzodiazepine-2,5'-[2*H*](5*H*)-oxazole) 4-Oxide (**35b**).

A mixture of 3 g of **19b**, 100 ml of 1,2-dichloroethane, 0.6 g of paraformaldehyde and 1.5 g of pivalic acid was heated to reflux with separation of water for 40 minutes. The reaction mixture was washed with saturated aqueous sodium bicarbonate, dried and evaporated. The residue was chromatographed over 60 g of silica gel using 5% (v/v) of ethanol in methylene chloride.

After elution of 80 mg of **23a**, the fractions containing **35b** were combined and evaporated. Crystallization from ethyl acetate/ether gave 0.88 g (28.5%) of colorless product with mp 189-191° dec; uv λ max 232 nm (ε 29,100), sh 260 (14,600), 300 (10,700), sh 345 (3900), nmr (deuteriochloroform + d-DMSO): δ 3.53 (s, 8 morpholine), 4.27 (s, 2, C_3-H), 5.2 (AB-system, J = 8.5 Hz, C_2-H), 6.6-7.6 (m, 8, aromatic H, NH).

Anal. Calcd. for $C_{21}H_{20}ClFN_4O_3$: C, 58.54; H, 4.68; N, 13.00. Found: C, 58.45; H, 4.79; N, 12.80.

7-Chloro-5-(2-fluorophenyl)-1,2-dihydro-2-[4-(iminomethyl)morpholinyl]-3*H*-1,4-benzodiazepine (**38**).

A mixture of 1.2 g (3 mmoles) of **19a**, 30 ml of ethanol, 30 ml of tetrahydrofuran, 0.1 methanolic ammonia (20%, v/v) and about 5 g of Raney nickel (type 28) was hydrogenated at atmospheric pressure for 3 hours. The catalyst was separated by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from ether gave 0.85 g (74%) of product. The analytical sample was recrystallized from tetrahydrofuran/hexane, mp 175-178°; uv: λ max 227 nm (ε 30,500), infl 265 (8000), 360 (2750).

Anal. Calcd. for $C_{20}H_{20}ClFN_4O$: C, 62.10; H, 5.21; N, 14.48. Found: C, 62.10; H, 5.33; N, 14.46.

Acknowledgement.

We are indebted to the following members of our Physical Chemistry Department for spectral and elemental analysis: Dr. W. Benz, Dr. F. Scheidl, Dr. W. Toome, Mr. S. Traiman, and Dr. T. Williams. We thank Dr. J. Blount and his staff for the X-ray analyses of compounds **11a** and **35b**.

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