Quinazolines and 1,4-Benzodiazepines. XCV [1]. Synthesis of 1,4-Benzodiazepines by Ring Expansion of 2-Chloromethylquinazolines with Carbanions

A. Walser*, T. Flynn, C. Mason and R. Ian Fryer

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

Received January 27, 1986

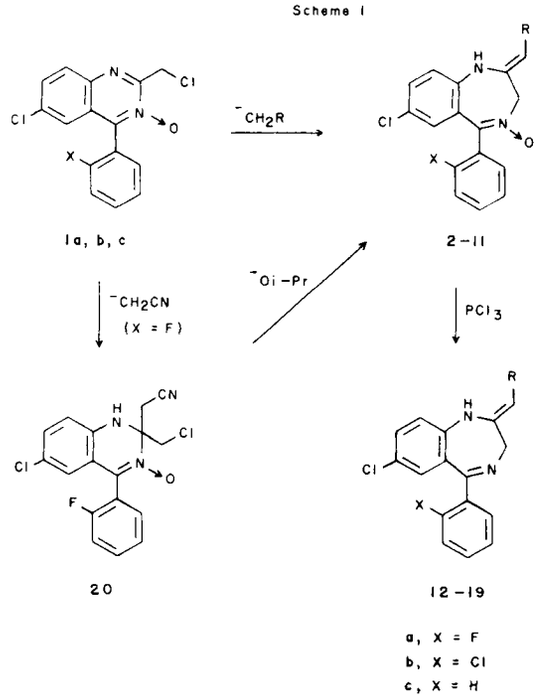
1,4-Benzodiazepines bearing a carbon substituent at the 2-position were obtained by reaction of 2-chloromethylquinazoline 3-oxides with stabilized carbanions. The carbanions of alkyl acetates, *N,N*-disubstituted acetamides, acetonitrile, dimethylsulfone, *N,N*-dimethyl methanesulfonamide and 2-methylpyridine were successfully applied. The conversion of some of the 2-carbon substituted 1,4-benzodiazepines to imidazo[1,5-*a*][1,4]benzodiazepines and [1,2,5]oxadiazino[5,4-*a*][1,4]benzodiazepines is described.

J. Heterocyclic Chem., **23**, 1303 (1986).

Sternbach [2] discovered that the reaction of the quinazoline 3-oxide **1c** with methylamine resulted in ring expansion to yield the 1,4-benzodiazepine chlordiazepoxide. Although other nucleophilic reagents such as hydroxide and alkoxides were subsequently found to effect the same ring expansion, the use of carbanions for this purpose has received little attention. After having shown that the anion of nitromethane effectively converted the quinazolines **1** to the 2-nitromethylene-1,4-benzodiazepines **2** [3], the application of this reaction to other stabilized carbanions was studied. The 2-substituted benzodiazepines were of interest to us as precursors for derivatives with a heterocyclic ring fused to the 1,2-bond, in particular imidazo[1,5-*a*][1,4] benzodiazepines [4].

The results listed in Table 1 demonstrate that a variety of stabilized primary carbanions were capable of effecting the Sternbach ring expansion, some of them in excellent yield. The anions of the reagents were generated with lithium diisopropylamide in tetrahydrofuran at temperatures ranging from -60 to $-40°$, depending on the stability of the carbanion. The best yields were obtained with the anions of *t*-butyl acetate. Reaction of **1** (X = F) with the anion of acetonitrile under similar conditions gave only small amounts of the desired benzodiazepine **8** and the

Scheme I



Scheme II

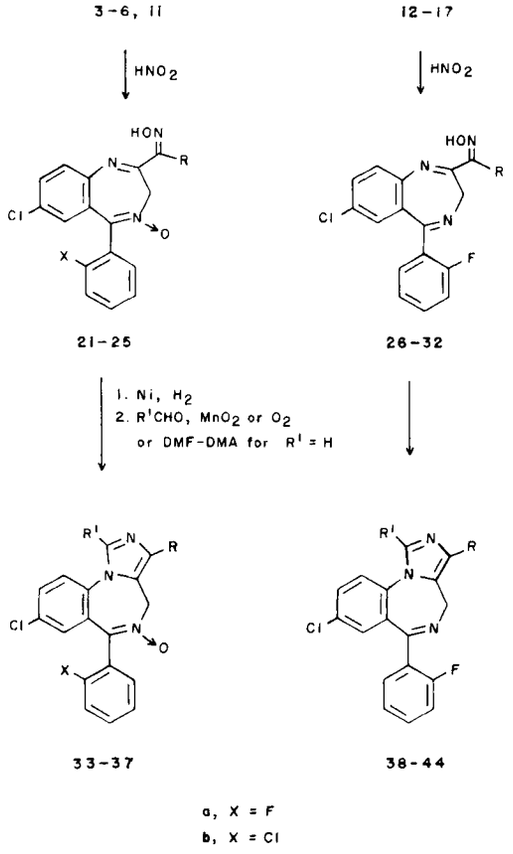


Table 1

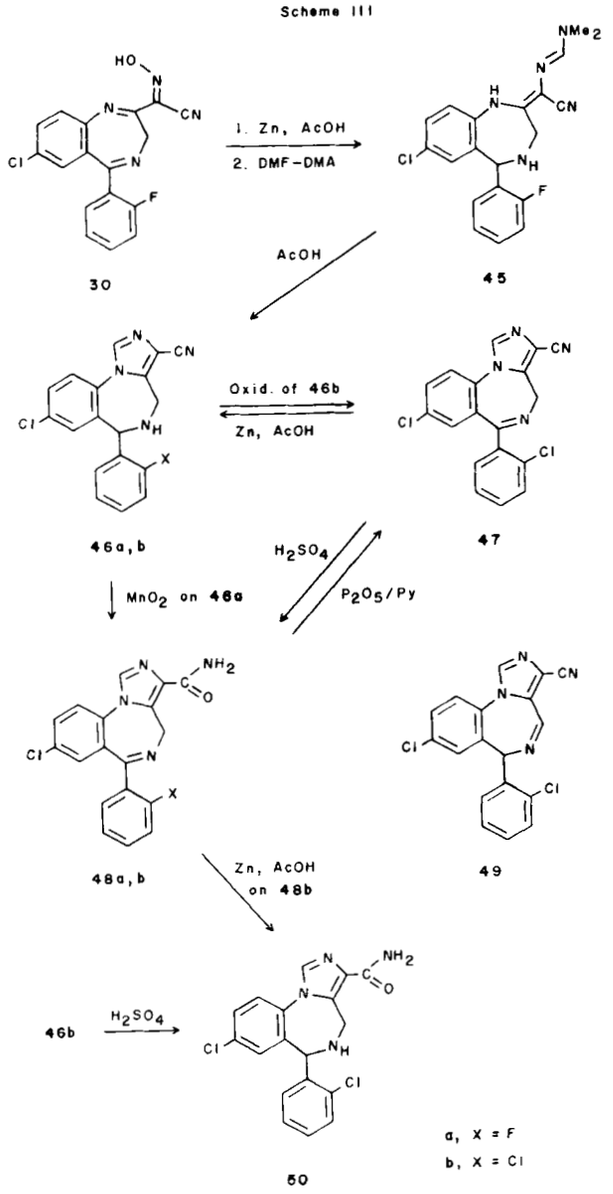
Compounds	Substituents R	X	Yield %	mp °C	Solvent of Recrystallization
2	NO_2	F	ref [3]		
3	COOEt	F	93	150-152	Ether
4	COOi-Pr	F	94	175-177	CH_2Cl_2/EtOH
5a	COOt-Bu	F	98	182-183	CH_2Cl_2/Hexane
5b	COOt-Bu	Cl	87	168-170	Ether
6a	$CONMe_2$	F	67	159-160	EtOH
6b	$CONMe_2$	Cl	66	222-225	EtOAc
6c	$CONMe_2$	H		221-223	CH_2Cl_2/EtOH
7	4-methylpiperazinocarbonyl	F	30	202-204	EtOH
8	CN	F	20	247-248	THF/EtOH
9a	SO_2NMe_2	F	61	168-170	EtOH/ether
9b	SO_2NMe_2	Cl	73	182-184	EtOAc/Hexane
10	SO_2Me	F	80	185-187	THF/EtOH
11	2-pyridyl	F	39	212-214	EtOAc
12	COOEt	F		109-111	EtOH
13	COOi-Pr	F		144-145	2-PrOH
14	COOt-Bu	F		158-160	Hexane
15a	$CONMe_2$	F		170-172	EtOH
15b	$CONMe_2$	Cl	71	176-178	EtOAc/Hexane
15c	$CONMe_2$	H		182-184	CH_2Cl_2/ether
16	CN	F	36	189-191	CH_2Cl_2/Hexane
17a	SO_2NMe_2	F	65	150-153	EtOAc/Hexane
17b	SO_2NMe_2	Cl	60	161-163	EtOH
18	SO_2Me	F	44	131-134	CH_2Cl_2/EtOH
19	2-pyridyl	F	79	169-172	CH_2Cl_2/Hexane

Table 2

Compound	Substituents R	X	Yield %	mp °C	Solvent of Recrystallization
21	COOEt	F	78	225-226	THF/EtOH
22	COOi-Pr	F	85	231-233	CH_2Cl_2/EtOH
23a	COOt-Bu	F	79	191-192	CH_2Cl_2/EtOH
23b	COOt-Bu	Cl	80	233-234 dec	2-PrOH
24	$CONMe_2$	H	73	254-255	THF/EtOH
25	2-pyridyl	F	67	191-193 dec	CH_2Cl_2/EtOH
26	COOEt		85	230-233	THF/EtOH
27	COOi-Pr		92	244-245	THF/2-PrOH
28	COOt-Bu		78	212-214	CH_2Cl_2/Hexane
29	$CONMe_2$		70	250-253	CH_2Cl_2/EtOH
30	CN		78	248-250	THF/EtOH
31	SO_2NMe_2		73	149-150	MeOH
32	2-pyridyl		71	220-222	MeOH

dihydroquinazoline **20** was isolated as the major product. This compound was converted to **8** by treatment with potassium *t*-butoxide in 2-propanol. This suggests that the anion of acetonitrile adds as expected to the 2-position of the quinazoline at low temperature but cannot effect the subsequent rearrangement during the warming of the reaction mixture to room temperature. We speculate that the acetonitrile anion is being destroyed during warm-up by condensation with a second molecule of acetonitrile. The ring expansions were carried out with three equivalents of carbanions to allow for the neutralization of the eliminated hydrogen chloride and the double deprotonation of the product. The reaction worked satisfactorily with the anions of dimethylsulfone, *N,N*-dimethylacetamide and *N,N*-dimethyl-methylsulfonamide, but the yields were mediocre for the compounds **7** and **11**.

Scheme III



30 45 46a,b 47 48a,b 49 50

The nitrones **3-6** and **8-11** were reduced to the corresponding imines by treatment with phosphorus trichloride, a standard reagent for this type of transformation. Both the nitrones **3-6** and **11** and the imines **12-17** and **19** were nitrosated as described previously [5] with sodium nitrite in glacial acetic acid to give the oximes **21-25** and **26-32** in good yields. (See data in Table 2). Nitrosation of the sulfones **10** and **18** failed. The reason for this failure was not uncovered. Hydrogenation of the oximes over Raney nickel in the presence of ammonia allowed reduction of the oxime functionality with retention of the nitrone. The imidazo[1,5-*a*][1,4]benzodiazepine-5-oxides were thus obtained by reacting the crude hydrogenation product with dimethylformamide dimethylacetal (for compounds **36** and **37**) or with acetaldehyde and manganese dioxide (for compounds **33-35**) (See Table 3).

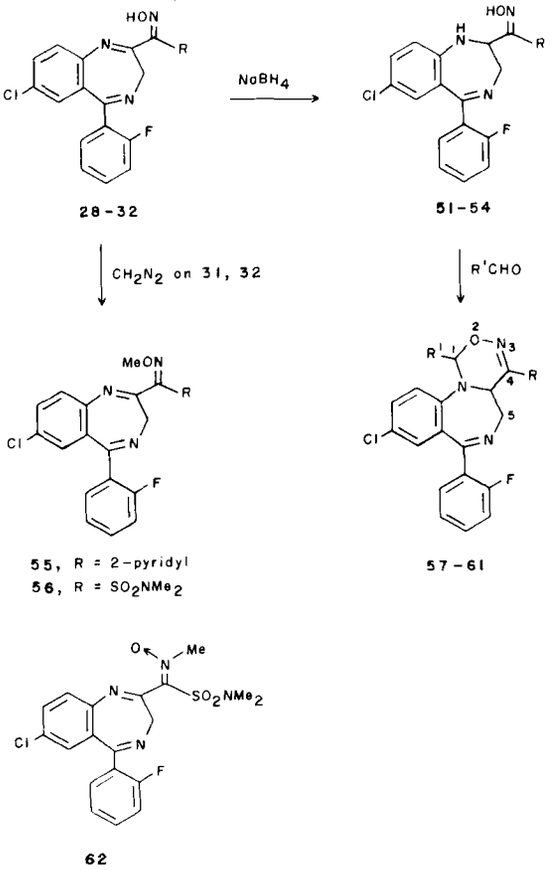
The same procedures were used for the preparation of the esters **38-42** and the dimethylamide **43**. The 1-ethoxycarbonyl derivative **44** was obtained by stirring a methylene chloride solution of the crude hydrogenation product of **28** with glyoxalic acid ethyl ester in the presence of air. Hydrogenation over palladium on carbon of **26** in the presence of acetaldehyde also led to the imidazobenzodiazepine **39**, although in lower yield. This catalyst thus not only reduced the oxime to the enediamine but also dehydrogenated the intermediate imidazoline to the imidazole.

We attempted to apply these methods for the conversion of the oximes **30-32** to the corresponding imidazobenzodiazepines. The hydrogenations of the cyanooxime **30**, the sulfonamide **31** and the pyridine derivative **32** led to complex mixtures. However, alternate methods for the elaboration of these intermediates into imidazobenzodiazepines were explored. Treatment of the cyanooxime **30** with zinc in acetic acid resulted in reduction to the desired enediamine with simultaneous saturation of the imine. The reduction product was not characterized but directly

Table 3

Compound	Substituents R	R'	X	Yield %	mp °C	Solvent of Recrystallization
33	COOEt	Me	F	51	225-227	EtOAc/MeOH
34	COOi-Pr	Me	F	71	206-208	EtOAc/MeOH
35	COOt-Bu	Me	F	52	272-274	CH_2Cl_2/Hexane
36	COOi-Pr	H	F	58	217-220 dec	THF/EtOAc
37a	COOt-Bu	H	F	38	277-279 dec	CH_2Cl_2/EtOAC
37b	COOt-Bu	H	Cl	61	255-257 dec	CH_2Cl_2/EtOAc
38	COOEt	Me		65	176-179 195-198	EtOAc/petr.ether
39	COOi-Pr	Me		58	200-202	EtOAc
40	COOt-Bu	Me		68	215-217	CH_2Cl_2/Hexane
41	COOi-Pr	H		73	183-185	EtOAc/Hexane
42	COOt-Bu	H		72	209-210	CH_2Cl_2/ether
43	$CONMe_2$	H		35	216-217	Ether
44	COOt-Bu	COOEt		53	195-196	EtOH/ether

Scheme IV



condensed with dimethylformamide dimethylacetal to give the amidine **45**. Ring closure of **45** to **46a** required heating in glacial acetic acid. (See Scheme III). Oxidation of **46a** with manganese dioxide in boiling 1,2-dichloroethane afforded the carboxamide **48a**, the nitrile apparently having undergone hydration to the amide under these conditions. The oxidation of the amine to the imine could be carried out with other reagents such as diethyl azodicarboxylate in refluxing toluene. As shown for the oxidation of the 2-chlorophenyl substituted analog **46b**, the double bond isomer **49** was formed in addition to **47** and the products were separated by chromatography. Interconversion of the amide and nitrile was possible by standard methods, hydration of **47** and **46b** with concentrated sulfuric acid yielded the amides **48b** and **50**, respectively, while dehydration of **48b** by means of phosphorus pentoxide in pyridine gave the nitrile **47**. Zinc in acetic acid cleanly reduced **48b** to **50**.

Another synthesis of imidazobenzodiazepines previously reported [6] involved the reaction of alpha-amino oximes of type **51-54** with aldehydes. The selective reduction of the 1,2-imine bond in compounds **28-32** was performed with sodium borohydride in ethanol (See data in Table 4 and reaction Scheme IV). Unlike compounds related to **51-54** in which R represents an electron donating substituent, compounds **51-54** condensed with formaldehyde and acetaldehyde in hot glacial acetic acid to give almost exclusively the corresponding oxadiazinobenzodiazepines **57-61**. The electron withdrawing quality of the substituent R in compounds **51-54** impeded the formation of the imidazobenzodiazepines by this method. The reaction of **51** with acetaldehyde in the presence of molecular sieves gave a mixture of two diastereomeric oxadiazinobenzodiazepines of which the major one was crystallized and fully characterized with exception of the stereochemistry.

We expected that methylation of the oxime oxygen in compounds **51-54** would enhance the electron density at the oxime nitrogen and block the formation of the oxadiazines and thus favor the ring closure to the imidazoles. Compounds **31** and **32** were therefore methylated with diazomethane. The pyridine **55** obtained by this reaction from **32** was then reduced with sodium borohydride in ethanol to the 1,2-dihydro derivative which was directly treated with paraformaldehyde and acetaldehyde in hot glacial acetic acid to yield the 3-(2-pyridyl) substituted imidazo[1,5-*a*] [1,4]benzodiazepines **63** and **64**, respectively. Diazomethane methylated the sulfonamide **31** both at the oxygen and the nitrogen of the oxime function and led to a mixture of **56** and **62**, separated by chromatography. Reduction of **56** with sodium borohydride gave a complex

Scheme V

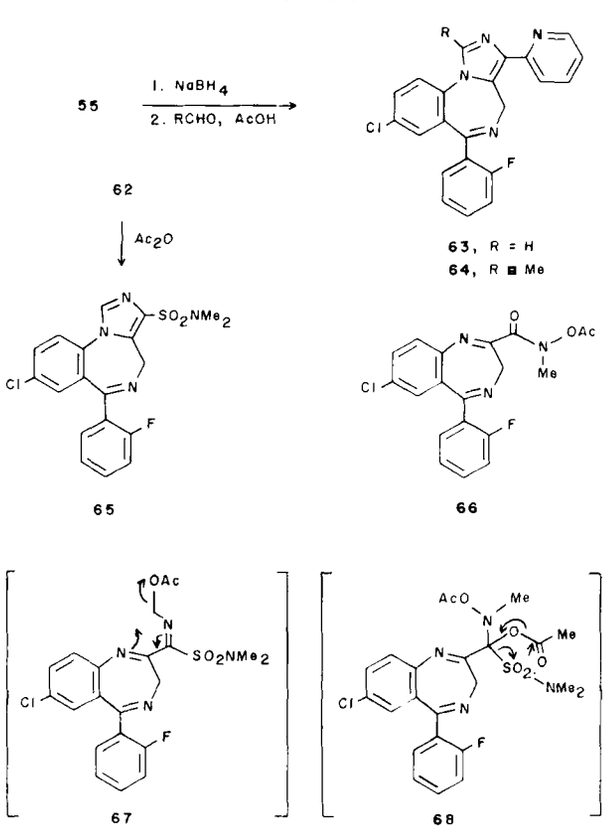


Table 4

Compounds	Substituents R	R'	Yield %	mp °C	Solvent of Recrystallization
51	COOt-Bu		37	203-204 dec	EtOAc
52	$CONMe_2$		50	214-215	CH_2Cl_2/EtOH
53	SO_2NMe_2		66	242-244	THF/EtOH
54	2-pyridyl		66	211-213	MeOH
57	COOt-Bu	H	45	216-217 dec	EtOH
58	$CONMe_2$	H	96	177-179	2-PrOH
59	SO_2NMe_2	H	26	240-242 dec	CH_2Cl_2/EtOAc
60	2-pyridyl	H	54	241-243	CH_2Cl_2/EtOAc
61	COOt-Bu	Me	44	196-197	Ether/Hexane

mixture unsuitable for further transformation to the desired imidazobenzodiazepine **65**. Compound **65** was obtained, however, by heating the nitrone **62** in refluxing acetic anhydride. The acetylated hydroxamic acid **66** was also isolated from this reaction. The formation of the imidazole **65** from the nitrone **62** may proceed through the rearrangement product **67** which could then ring close as indicated and aromatize by loss of a proton. The acetylated hydroxamic acid **66** may arise from acetylation of the nitrone oxygen in **62** followed by addition of acetate to give the possible intermediate **68**. Elimination of *N,N*-dimethylacetamide and sulfur dioxide from **68** as indicated could then lead to the observed product **66**.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Carey Model 14 spectro-photometer. 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. The yields of most experiments were not optimized.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylideneacetic Acid Ethyl Ester 4-Oxide (**3**) [7].

A solution of *n*-butyllithium in hexane, 0.3 mole, was added at −50° to 200 ml of a 2-molar solution of diisopropylamine in dry tetrahydrofuran mixed under an atmosphere of nitrogen. Ethyl acetate, 40 ml, was added slowly at −50° to −45°. After complete addition a solution of 32.5 g (0.1 mole) of 6-chloro-2-chloromethyl-4-(2-fluorophenyl)quinazoline 3-oxide (**1a**) [3] in 200 ml of tetrahydrofuran was poured in and the reaction mixture was stirred for 2 hours while allowing it to warm to room temperature. It was acidified by addition of 30 ml of acetic acid and was partitioned between water and methylene chloride/toluene. The organic phase was washed with brine, dried and evaporated. The crystalline residue was collected with ether to yield 34.5 g (93%) of product with mp 150-152°.

Using isopropyl acetate and *t*-butyl acetate in place of ethyl acetate the following esters were prepared in the same fashion:

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylideneacetic Acid Isopropyl Ester 4-Oxide (**4**).

This compound was obtained in 94% yield with mp 175-177°, crystallized from methylene chloride/ethanol.

Anal. Calcd. for $C_{20}H_{18}ClFN_2O_3$: C, 61.78; H, 4.67; N, 7.20. Found: C, 61.85; H, 4.83; N, 7.01.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylideneacetic Acid *t*-Butyl Ester 4-Oxide (**5a**).

This compound was obtained in 98% yield with mp 182-183°, crystallized from methylene chloride/hexane.

Anal. Calcd. for $C_{21}H_{20}ClFN_2O_3$: C, 62.61; H, 5.00; N, 6.95. Found: C, 62.73; H, 4.77; N, 6.83.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylideneacetic Acid *t*-Butyl Ester 4-Oxide (**5b**).

This compound was similarly prepared by reacting 6-chloro-2-chloromethyl-4-(2-chlorophenyl)quinazoline 3-oxide (**1b**) [8] with the anion of *t*-butyl acetate. It was obtained in 87% yield and had mp 168-170°, crystallized from ether.

Anal. Calcd. for $C_{21}H_{20}Cl_2N_2O_3$: C, 60.15; H, 4.81; N, 6.68. Found: C, 60.12; H, 4.80; N, 6.66.

[7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]-*N,N*-dimethylacetamide 4-Oxide (**6b**).

A 2-molar solution of diisopropylamine in tetrahydrofuran, 40 ml (0.08 mole), was stirred under nitrogen and cooled to −60°. A solution of *n*-butyllithium in hexane, 0.065 mole, was added followed by 7.4 ml (0.08 mole) of *N,N*-dimethylacetamide, keeping the temperature below −50°. After stirring for 5 minutes a solution of 6.8 g (0.02 mole) of quinazoline **1b** in 40 ml of tetrahydrofuran was poured in all at once. The cooling bath was removed and stirring was continued for 1 hour. The mixture was acidified with acetic acid and diluted with saturated aqueous sodium-bicarbonate solution. The product was extracted with methylene chloride and the extracts were dried and evaporated. Crystallization from ether gave 5.2 g (66%) of crystals with mp 211-214°. The analytical sample recrystallized from ethyl acetate to give colorless product with mp 222-225°; nmr (deuteriochloroform): 3.05 (s, 6, $N(CH_3)_2$), 4.6 (s, 2, C_3-H), 5.25 (s, 1, =CH-) 6.83 (d, 1, J = 2 Hz, C_6-H), 7.03 (d, 1, J = 9 Hz, C_9-H), 7.1-7.6 (m, 5, aromatic H), 12.0 (broads, 1, NH).

Anal. Calcd. for $C_{19}H_{17}Cl_2N_3O_2$: C, 58.47; H, 4.39; N, 10.77. Found: C, 58.48; H, 4.38; N, 10.66.

[7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]-*N,N*-dimethylacetamide 4-Oxide (**6a**).

The analogous reaction of **1a** with the anion of *N,N*-dimethylacetamide gave **6a** in 67% yield. After recrystallization from ethanol it had mp 159-160°.

Anal. Calcd. for $C_{19}H_{17}ClFN_3O_2$: C, 61.05; H, 4.58; N, 11.24. Found: C, 61.05; H, 4.62; N, 11.13.

[7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ylidene]-*N,N*-dimethylacetamide 4-Oxide (**6c**).

This compound was similarly obtained by reaction of 6-chloro-2-

chloromethyl-4-phenylquinazoline 3-oxide (**1c**) [2] with the anion of dimethylacetamide. The analytical sample was recrystallized from methylene chloride/ethanol and had mp 221-223°.

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.14; H, 5.10; N, 11.81. Found: C, 64.17; H, 5.01; N, 11.64.

2-[7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-ylidene]-1-(4-methyl-1-piperazinyl)ethanone 4-Oxide (**7a**).

The quinazoline **1a** was reacted as described above with the anion generated in the same fashion from 1-acetyl-4-methylpiperazine. The reaction mixture quenched by addition of dry ice and was partitioned between toluene and aqueous sodium bicarbonate. The organic phase was dried and evaporated and the residue was chromatographed over 20-fold amount of silica gel using 5% (v/v) of ethanol in methylene chloride. Crystallization from ethanol yielded 30% of product with mp 202-204°; nmr (deuteriochloroform): 2,3 (s, 3, NCH_3) 2.42 (m, 4, NCH_2), 3.65 (m, 4, $CONCH_2$), 4.6 (s, 2, C_3-H), 5.3 (s, 1, -CH=) 6.8-7.6 (m, 7, aromatic H), 11.8 (s, 1, NH).

Anal. Calcd. for $C_{22}H_{22}ClFN_4O_2$: C, 61.61; H, 5.17; N, 13.06. Found: C, 61.84; H, 5.35; N, 13.07.

[7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylidene]-acetonitrile 4-Oxide (**8**).

The anion of acetonitrile was generated in the same way at −50° and reacted with 32.5 g (0.1 mole) of the quinazoline **1a**. The crude product obtained after the workup described above was dissolved in 300 ml of isopropanol and the solution was treated with 20 g (0.178 mole) of potassium *t*-butoxide. After stirring at room temperature for 0.5 hour the mixture was acidified with acetic acid and diluted with water. The crystalline precipitated product was filtered off, washed with water and sucked dry. Recrystallization from methylene cloride/tetrahydrofuran/-ethanol gave 6.4 g (20%) of product with mp 247-248°; nmr (d-DMSO): mixture of two isomers 4.4-5.1 (m, 3, C_3-H and -CH=), 6.74 (d, 1, J = 2 Hz, C_6-H), 7.0-7.8 (m, 6, aromatic H), 10.7 (s, 1, NH).

Anal. Calcd. for $C_{17}H_{11}ClFN_3O$: C, 62.30; H, 3.38; N, 12.82. Found: C, 62.17; H, 3.51; N, 12.94.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2-([(dimethylamino)sulfonyl]-methylene)-2*H*-1,4-benzodiazepine 4-Oxide (**9a**).

A solution of 73.8 g (0.6 mole) of *N,N*-dimethyl methanesulfonamide in 300 ml of tetrahydrofuran was added dropwise to a solution of 0.6 mole of lithium diisopropylamide at −60°. After complete addition stirring was continued for 5 minutes and a solution of 48.5 g (0.15 mole) of **1a** in 400 ml of tetrahydrofuran was added all at once. Cooling was discontinued and the mixture was stirred for 45 minutes. After the usual workup (extraction with toluene), the product was crystallized from ethanol/ether to give 39 g (61%) of crystals with mp 168-170°. The analytical sample was recrystallized from ethyl acetate/ether and had the same mp; nmr (deuteriochloroform): 2.75 (s, 6, $N(CH_3)_2$), 4.56 (s, 2, C_3-H), 5.1 (s, 1, -CH=), 6.9-7.7 (m, 7, aromatic H), 9.28 (s, 1, NH).

Anal. Calcd. for $C_{18}H_{17}ClFN_3O_3S$: C, 52.75; H, 4.18; N, 10.25. Found: C, 52.72; H, 4.26; N, 10.56.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2-([dimethylamino)sulfonyl]-methylene)-2*H*-1,4-benzodiazepine 4-Oxide (**9b**).

This compound was similarly prepare in 73% yield by reaction of **1b** with the anion of *N,N*-dimethyl methanesulfonamide. Crystallization and recrystallization from ethyl acetate/hexane gave colorless product with mp 182-184°.

Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O_3S$: C, 50.71; H, 4.02; N, 9.86. Found: C, 50.77; H, 4.07; N, 9.92.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-2-[(methylsulfonyl)methyl-ene]-1*H*-1,4-benzodiazepine 4-Oxide (**10**).

The anion of dimethyl sulfone was generated as described above with lithium diisopropylamide at −50° and reacted with the quinazoline **1a**. After the usual workup and extraction with toluene the product was crystallized from ethyl acetate/ether to yield 80% with mp 180-181°. Recrystallization for analysis from tetrahydrofuran/ethanol gave product with mp 185-187°C; uv: sh 220 (25000), sh 240 (21500) max 282 (38400) sh 355 (2200); nmr (deuteriochloroform): mixture of two isomers, most likely tautomers 3.07 and 3.17 (2 s, 3, CH_3) 4.36 (s, 0.85, CH_2SO_2), 4.52 (s, 1.45 C_3-H), 4.75 (s, 0.85, C_3-H), 5.26 (s, 0.7, -CH=), 6.9-7.7 (m, 7, aromatic H), 9.55 (broad s, 0.7, NH).

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_3S$): C, 53.62; H, 3.71; N, 7.36. Found: C, 53.71; H, 3.83; N, 7.02.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-2-[(2-pyridyl)methylene]-1*H*-1,4-benzodiazepine 4-Oxide (**11**).

Reaction of 16.1 g (0.05 mole) of the quinazoline **1a** with the anion of 2-picoline generated as described above yielded after the standard workup and crystallization from 2-propanol 7.3 g (39%) of product with mp 201-204° dec. Recrystallization from ethyl acetate for analysis gave yellow crystals with mp 212-214° dec; uv: max 227 nm (23100), sh 236 (21900), 283 (25500), 384 (27000) sh 405 (3100); ir (chloroform): 1650 cm^{-1}; nmr (deuteriochloroform): 4.67 (s, 2, C_3-H), 5.49 (s, 1, -CH=), 6.8-7.8 (m, 10, aromatic H), 8.42 (m, 1, C_6-H of pyridine ring), 12.1 (s, 1, NH).

Anal. Calcd. for $C_{21}H_{15}ClFN_3O$: C, 66.41; H, 3.98; N, 11.06. Found: C, 66.40; H, 4.00; N, 11.02.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-bezodiazepine-2-ylidene-acetic Acid Ethyl Ester (**12**).

Phosphorus trichloride 10 ml, was added to a solution of 10 g (0.0266 mole) of **3** in 100 ml of methylene chloride. After standing at room temperature for 3 hours, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was separated, dried and evaporated. The crude product was directly used for nitrosation in the next step. For the purpose of characterization a sample was purified by filtering over a pad of silica gel using 10% (v/v) of ethyl acetate in methylene chloride. Crystallization from ethanol gave colorless crystals with mp 109-111°.

Anal. Calcd. for $C_{19}H_{16}ClFN_2O_2$: C, 63.60; H, 4.49; N, 7.81. Found: C, 63.66; H, 4.30; N, 7.98.

In the same fashion were prepared:

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylidene-acetic Acid Isopropyl Ester (**13**).

This compound crystallized from 2-propanol, mp 144-145°.

Anal. Calcd. for $C_{20}H_{18}ClFN_2O_2$: C, 64.43; H, 4.87; N, 7.51. Found: C, 64.54; H, 4.97; N, 7.43.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-ylidene-acetic Acid *t*-Butyl Ester (**14**).

This compound crystallized from hexane, mp 158-160°.

Anal. Calcd. for $C_{21}H_{20}ClFN_2O_2$: C, 65.19; H, 5.21; N, 7.24. Found: C, 65.45; H, 5.11; N, 7.07.

[7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]-*N,N*-dimethylacetamide (**15b**).

A solution of 2.5 g (6.4 mmoles) of **6b** in 100 ml of methylene chloride was treated with 2.5 ml (28 mmoles) of phosphorus trichloride and stirred for 30 minutes. The mixture was washed with sodium carbonate solution, dried and evaporated. The residue was passed over a pad of silica gel using 10% (v/v) of ethyl acetate in hexane. Crystallization of the clean eluate from ethyl acetate/hexane yielded 1.7 g (71%) of product with mp 176-178°; nmr (deuteriochloroform): 3.0 (s, 6, NMe_2), 4.4 (s, 2, C_3-H), 5.07 (s, 1, -CH=), 6.8-7.6 (m, 7, aromatic H), 11.9 (s, 1, NH).

Anal. Calcd. for $C_{19}H_{17}Cl_2N_3O$: C, 60.97; H, 4.58; N, 11.23. Found: C, 61.12; H, 4.77; N, 11.10.

In the same manner were obtained:

[7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]-*N,N*-dimethylacetamide (**15a**).

This compound had mp 170-172° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{17}ClFN_3O$: C, 63.78; H, 4.79; N, 11.74. Found: C, 63.71; H, 4.78; N,11.70.

[7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ylidene]-*N*,*N*-dimethylacetamide (**15c**).

This compound had mp 182-184° following recrystallization from methylene chloride/ether.

Anal. Calcd. for $C_{19}H_{18}ClN_3O$: C, 67.16; H, 5.34; N, 12.37. Found: C, 67.23; H, 5.41; N, 12.01.

[7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ylidene]acetonitrile (**16**).

Treatment of 5.9 g (18 mmoles) of **8** in 750 ml of methylene chloride with 12 ml (137 mmoles) of phosphorus trichloride for 3 hours at room temperature yielded after the usual workup followed by chromatography over silica gel with methylene chloride yielded 2 g (36%) of product. It was recrystallized from ethanol for analysis and had mp 189-191°.

Anal. Calcd. for $C_{17}H_{11}ClFN_3$: C, 65.60; H, 3.56; N, 13.48. Found: C, 65.53; H, 3.52; N, 13.66.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2[(dimethylaminosulfonyl)methylene]-2*H*-1,4-benzodiazepine (**17a**).

This compound was obtained in 65% yield by reduction of **9a** with phosphorus trichloride and chromatography over a pad of silica gel using ethyl acetate/methylene chloride 1:1 (v/v). Crystallization from ethyl acetate/hexane and recrystallization from the same solvents gave product with mp 150-153°; nmr (deuteriochloroform): 2.72 (s, 6, NMe_2), 4.37 (s, 2, C_3-H), 4.9 (s, 1, -CH=), 6.9-7.7 (m, 7, aromatic H), 9.16 (broad s, 1, NH).

Anal. Calcd. for $C_{18}H_{17}ClFN_3O_2S$: C, 54.89; H, 4.35; N, 10.67. Found: C, 54.96; H, 4.33; N, 10.69.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2-[(dimethylaminosulfonyl)-methylene]-2*H*-1,4-benzodiazepine (**17b**).

This compound was prepared in 60% yield from **9b**. It was crystallized and recrystallized from ethanol, mp 161-163°.

Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O_2S$: C, 52.69; H, 4.18; N, 10.24. Found: C, 52.76; H, 4.15; N, 10.05.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2-[(methylsulfonyl)methylene]-2*H*-1,4-benzodiazepine (**18**).

A mixture of 5 g (13.1 mmoles) of **10**, 100 ml of tetrahydrofuran and 50 ml of methylene chloride and 5 ml (57 mmoles) of phosphorus trichloride was stirred for 40 minutes at room temperature. After dilution with methylene chloride the solution was washed with 10% aqueous sodium carbonate containing 10 ml of ammonia. The organic layer was dried and evaporated. The residue was chromatographed over 100 g of silica gel using 10% of ethyl acetate in methylene chloride for elution. The clean fractions were combined and evaporated and the residue was crystallized from ether to yield 2.1 g (44%) of product which was recrystallized from methylene chloride/ethanol for analysis, mp 131-134°; uv: max 263 nm (22600), 287 (2400), 343 (2500); nmr (deuteriochloroform): 3.0 (s, 3, CH_3), 4.33 (s, 2, C_3-H), 5.1 (s, 1, -CH=) 6.8-7.8 (m, 7, aromatic H), 9.33 (broad s, 1, NH) about 15% of the other tautomer was also detected.

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_2S$: C, 55.97; H, 3.87; N, 7.68. Found: C, 56.00; H, 3.83; N, 7.72.

7-Chloro-5-(2-florophenyl)-2,3-dihydro-2-[(2-pyridyl)methylene]-1*H*-1,4-benzodiazepine (**19**).

A solution of 10 g (26 mmoles) of **11** in 250 ml of methylene chloride and 250 ml of tetrahydrofuran was stirred at room temperature for 15 minutes with 10 ml of phosphorus trichloride. After the usual workup the product was crystallized and recrystallized twice from methylene chloride/ethanol to leave 7.6 g (79%) with mp 168-171°. The analytical sample was recrystallized again from methylene chloride/hexane and left yellow crystals with mp 169-171°; nmr (deuteriochloroform): 4.5 (s, 2, C_3-H), 5.3 (s, 1, -CH=), 6.8-7.8 (m, 10, aromatic H), 8.45 (m, 1, C_6-H of pyridine), 12.0 (broad s, 1, NH).

Anal. Calcd. for $C_{21}H_{15}ClFN_3$: C, 69.33; H, 4.16; N, 11.55. Found: C, 69.28; H, 4.9; N, 11.45.

6-Chloro-2-chloromethyl-4-(2-fluorophenyl)-1,2-dihydroquinazoline-2-acetonitrile 3-Oxide (**20**).

A 2-molar solution of diisopropylamine in tetrahydrofuran, 20 ml (40 mmoles) was diluted with 10 ml of tetrahydrofuran and cooled to −50°. A solution of 30 mmole of butyllithium in hexane was then added followed by 3 ml of acetonitrile keeping the temperature at −50°. A solution of 3.2 g (10 mmoles) of **1a** in 40 ml of tetrahydrofuran was then added all at once and the reaction mixture was allowed to warm to room temperature. After acidifying with 5 ml of acetic acid, the mixture was diluted with water and was extracted with toluene. The extracts were washed with saturated sodium bicarbonate solution, dried and evaporated. The residue was chromatographed over 120 g of silica gel using 20% (v/v) of ethyl acetate in methylene chloride for elution. The fractions containing the major component were combined and evaporated and the residue was crystallized from ethyl acetate/ether to give 1.1 g (30%) of yellow product with mp 162-164°; nmr (d-DMSO): *ca.* 1:1 mixture of two conformers.

Anal. Calcd. for $C_{17}H_{12}Cl_2FN_3O$: C, 56.06; H, 3.32; N, 11.54. Found: C, 56.10; H, 3.31; N, 11.45.

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroximino-3*H*-1,4-benzodiazepine-2-acetic Acid Ethyl Ester 4-Oxide (**21**).

Sodium nitrite, 1.6 g (23 mmoles), was added over a period of 5 minutes to a suspension of 7.5 g (20 mmoles) of **3** in 30 ml of glacial acetic acid. After stirring for 15 minutes at room temperature the mixture was diluted with water, 30 ml, to complete the crytallization of the product. The solids were collected, washed with water, ethanol and ether and recrystallized from tetrahydrofuran/ethanol to give 6.2 g (78%) of light yellow crystals with mp 225-226°.

Anal. Calcd. for $C_{19}H_{15}ClFN_3O_4$: C, 56.52; H, 3.74; N, 10.41. Found: C, 56.79; H, 3.87; N, 10.28.

The following esters were prepared analogously:

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid Isopropyl Ester 4-Oxide (**22**).

This compound was obtained by nitrosation of **4**, crystallized from methylene chloride/ethanol, mp 231-233°, in 85% yield.

Anal. Calcd. for $C_{20}H_{17}ClFN_3O_4$: C, 57.49; H, 4.10; N, 10.06. Found: C, 57.16; H, 4.20; N, 9.91.

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid *t*-Butyl Ester 4-Oxide (**23a**).

This compound was obtained in 79% yield by nitrosation of **5a**, crystallized from methylene chloride/ethanol, mp 191-192°.

Anal. Calcd. for $C_{21}H_{19}ClFN_3O_4$: C, 58.41; H, 4.43; N, 9.73. Found: C, 58.62; H, 4.22; N, 9.54.

7-Chloro-5-(2-chlorophenyl)-*alpha*-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid *t*-Butyl Ester 4-Oxide (**23b**).

This compound was obtained in 80% yield by nitrosation of **5b**, crystallized from 2-propanol, mp 233-234°.

Anal. Calcd. for $C_{21}H_{19}Cl_2N_3O_4$: C, 56.26; H, 4.27; N, 9.37. Found: C, 56.18; H, 4.50; N, 9.13.

7-Chloro-*alpha*-(hydroxyimino)-*N*,*N*-dimethyl-5-phenyl-3*H*-1,4-benzodiazepine-2-acetamide 4-Oxide (**24**).

A solution of 2.2 g (7.9 mmoles) of **6c** in 10 ml of acetic acid was treated with 0.71 g (10.2 mmoles) of sodium nitrite and stirred for 1 hour. The product was precipitated by addition of water, was filtered off, washed with water and sucked dry. It was dissolved in methylene chloride containing 10% of ethanol and the solution was dried and evaporated. Recrystallization from tetrahydrofuran/ethanol yield 2.2 g (73%) of yellowish crystals with mp 254-255°.

Anal. Calcd. for $C_{19}H_{17}ClN_4O_3$: C, 59.30; H, 4.45; N, 14.56. Found: C, 58.99; H, 4.58; N, 14.60.

[7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-yl]-2-pyridylmethanone Oxime 4-Oxide 0.66 Molar Ethanol Solvate (**25**).

Nitrosation of 3 g (7.9 mmoles) of **11** with 0.71 g (10.2 mmoles) of sodium nitrite as described above yielded 2.4 g (67%) of product which crystallized from methylene chloride/ethanol as a solvate with mp 191-193° dec. According to nmr and microanalysis the crystals contained 0.66 mole of ethanol; nmr (d-DMSO): 1.07 (t, J = 6.5 Hz, ethanol), 3.4 (m, ethanol), 5.08 (broad s, 2, C_3-H), 6.9 (d, 1, J = 2 Hz, C_6-H), 7.1-8.2 (m, 9, aromatic H), 8.56 (m, 1, C_6-H of pyridine).

Anal. Calcd. for $C_{21}H_{14}ClFN_4O_2 \cdot 0.66\ C_2H_6O$: C, 60.73; H, 4.43; N, 12.32. Found: C, 60.85; H, 4.14; N, 12.58.

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid Ethyl Ester (**26**).

The crude **12** obtained by reduction of 10 g of **3** with phosphorus trichloride was dissolved in 40 ml of acetic acid. Sodium nitrite, 2.45 g, was added and the mixture was stirred for 15 minutes at room temperature. The product started to crystallize and was further precipitated by addition of 50 ml of water. The crystals were collected, washed with water, ethanol and ether to yield 8.8 g (85%) of product. The analytical sample was recrystallized from tetrahydrofuran/ethanol to give pale yellow crystals with mp 230-233°.

Anal. Calcd. for $C_{19}H_{15}ClFN_3O_3$: C, 58.85; H, 3.90; N, 10.84. Found: C, 59.02; H, 3.93; N, 10.63.

The following oximes were similarly prepared:

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid Isopropyl Ester (**27**).

This compound was obtained by nitrosation of **13**, crystallized from tetrahydrofuran/ethanol, light yellow crystals with mp 244-245°, 92% yield.

Anal. Calcd. for $C_{20}H_{17}ClFN_3O_3$: C, 59.78; H, 4.26; N, 10.46. Found: C, 59.85; H, 4.29; N, 10.48.

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-3*H*-1,4-benzodiazepine-2-acetic Acid *t*-Butyl Ester (**28**).

This compound was obtained in 78% yield by nitrosation of **14**, crystallized from methylene chloride/hexane, mp 212-214°.

Anal. Calcd. for $C_{21}H_{19}ClFN_3O_3$: C, 60.65; H, 4.61; N, 10.10. Found: C, 60.89; H, 4.57; N, 10.48.

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-*N*,*N*-dimethyl-3*H*-1,4-benzodiazepine-2-acetamide (**29**).

This compound was obtained in 70% yield by reduction of **6a** with phosphorus trichloride followed by nitrosation of the crude **15a** with sodium nitrite. Recrystallization from methylene chloride/ethanol gave light yellow crystals with mp 250-253°.

Anal. Calcd. for $C_{19}H_{16}ClFN_4O_2$: C, 59.00; H, 4.17; N, 14.48. Found: C, 58.90; H, 4.01; N, 14.12.

7-Chloro-5-(2-fluorophenyl)-*alpha*-hydroxyimino-3*H*-14-benzodiazepine-2-acetonitrile (**30**).

This compound was obtained in 78% yield by nitrosation of **16**, recrystallized from tetrahydrofuran/ethanol mp 248-250°.

Anal. Calcd. for $C_{17}H_{10}ClFN_4O$: C, 59.92; H, 2.96; N, 16.44. Found: C, 59.78; H, 3.09; N, 16.23.

7-Chloro-5-(2-fluorophenyl)-*N*,*N*-dimethyl-3*H*-1,4-benzodiazepine-2-(*N'*-hydroxy)iminomethylsulfonamide (**31**).

This compound was obtained in 73% yield by nitrosation of **17a**, recrystallized from methanol, mp 149-150°; nmr (deuteriochloroform + d-DMSO): 2.9 (s, 6, NMe_2), 4.27 (broad s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H), *ca.* (broad s, 1, OH).

Anal. Calcd. for $C_{18}H_{16}ClFN_4O_3S$: C, 51.13; H, 3.81; N, 13.26. Found: C, 51.01; H, 3.62; N, 12.98.

[7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-yl]-2-pyridylmethanone Oxime (**32**).

This compound was obtained in 71% yield by nitrosation of **19**. After dilution with water the reaction mixture was extracted with methylene chloride. The product was crystallized from ethanol and recrystallized for analysis from methanol to give pale yellow crystals with mp 220-222°; nmr (d-DMSO): 4.5 (very broad s, 2, C_3-H), 7.0-8.0 (m, 10, aromatic H) 8.5 (m, 1, C_6-H of pyridine) 12.1 (broad s, 1, OH).

Anal. Calcd. for $C_{21}H_{14}ClFN_4O$: C, 64.61; H, 3.59; N, 14.26. Found: C, 64.19; H, 3.46; N, 14.45.

8-Chloro-6-(2-fluoropheyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4-]benzodiazepine-3-carboxylic Acid Ethyl Ester 5-Oxide (**33**).

A mixture of 2 g (5 mmoles) of **21**, 100 ml of tetrahydrofuran, 30 ml of ethanol, 2 g of Raney nickel and 0.5 ml of methanol containing 20% (v/v) of ammonia was hydrogenated at atmospheric pressure for 2 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 30 ml of methylene chloride and treated with 0.6 ml of acetaldehyde. After stirring for 15 minutes at room temperature 2 g of activated manganese dioxide was added and stirring was continued for 15 minutes. The manganese dioxide was separated by filtration over celite and the filtrate was evaporated. Crystallization of the residue from ethyl acetate/ether yielded 1.05 g (51%) of product which was recrystallized from ethyl acetate/methanol for analysis to leave off white crystals with mp 225-227°.

Anal. Calcd. for $C_{21}H_{17}ClFN_3O_3$: C, 60.95; H, 4.14; N, 10.15. Found: C, 60.83; H, 3.93; N, 9.98.

By the same procedure were prepared:

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4-]benzodiazepine-3-carboxylic acid isopropyl ester 5-oxide (**34**).

This compound was obtained in 71% yield from compound **22**, crystrallized from ethyl acetate/methanol, mp 206-208°.

Anal. Calcd. for $C_{22}H_{19}ClFN_3O_3$: C, 61.76; H, 4.48; N, 9.82. Found: C, 61.90; H, 4.43; N, 9.69.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*]benzodiazepine-3-carboxylic Acid *t*-Butyl Ester 5-Oxide (**35**).

This compound was obtained in 52% yield from compound **23a**, crystallized from methylene chloride/hexane, mp 272-274°.

Anal. Calcd. for $C_{23}H_{21}ClFN_3O_3$: C, 62.51; H, 4.79; N, 9.50. Found: C, 62.65; H, 4.65; N, 9.55.

8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Isopropyl Ester 5-Oxide (**36**).

A mixture of 12.6 g (30 mmoles) of **22**, 225 ml of tetrahydrofuran, 50 ml of 2-propanol, 12.5 g of Raney nickel and 3 ml of methanol containing 20% (v/v) of ammonia was hydrogenated at atmospheric pressure for 3.5 hours. The catalyst was separated by filtration over celite and the filtrate was evaporated. The residue was dissolved in 200 ml of methylene chloride and the solution was treated with 6 ml of dimethylformamide diethylacetal and 12 g of silica gel. After stirring at room temperature for 3 hours, the silica gel was filtered off and the filtrate was evaporated. Crystallization of the residue from ethyl acetate/ether gave 7.2 g (58%) of product which was recrystallized from analysis from tetrahydrofuran/-ethyl acetate to leave colorless crystals with mp 217-220° dec; nmr (deuteriochloroform): 1.42 (d, J = 6 Hz, 6, Me_2), 5.32 (m, 1, $CHMe_2$), *ca.* 5.15 (broad d) and *ca.* 6.15 (broad d) AB-system, 2, C_4-H), 7.0-7.8 (m, 7, aromatic H), 8.03 (s, 1, C_1-H).

Anal. Calcd. for $C_{21}H_{17}ClFN_3O_3$: C, 60.95; H, 4.14; N, 10.15. Found: C, 60.95; H, 4.05; N, 10.23.

By the same method were obtained:

8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid *t*-Butyl Ester 5-Oxide (**37a**).

This compound was obtained in 38% yield from **23a**, crystallized from methylene chloride/ethyl acetate, mp 277-279° dec.

Anal. Calcd. for $C_{22}H_{19}ClFN_3O_3$: C, 61.76; H, 4.48; N, 9.82. Found: C, 61.90; H, 4.70; N, 9.65.

8-Chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid *t*-Butyl Ester 5-Oxide (**37b**).

This compound was obtained in 61% yield from **23b**, crystallized from methylene chloride/ethyl acetate, mp 255-257°.

Anal. Calcd for $C_{22}H_{19}Cl_2N_3O_3$: C, 59.47; H, 4.31; N, 9.45. Found: C, 59.38; H, 4.41; N, 9.37.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Ethyl Ester (**38**).

A. A mixture of 15.5 g (40 mmoles) of **26**, 400 ml of tetrahydrofuran, 40 ml of ethanol, 15. 5 g of Raney nickel and 4 ml of methanol containing 20% (v/v) of ammonia was hydrogenated at atmospheric pressure for 5.5 hours when hydrogen consumption had ceased. The catalyst was separated and the filtrate was evaporated. The residue was dissolved in 200 ml of methylene chloride and treated with 4 ml of acetaldehyde. After stirring for 20 minutes, 15.5 g of activated manganese dioxide was added and stirring was continued for 30 minutes. The residue obtained after filtration and evaporation was crystallized from ether over night to yield 10.4 g (65%) of tan product with mp 174-176°. The analytical sample was recrystallized from ethyl acetate/petr. ether to give off white crystals with mp 176-179°. A higher melting crystalline modification with mp 195-198° was also observed; nmr (deuteriochloroform): 1.38 (t, J = 6.5 Hz, 3, CH_3), 2.55 (s, 3, CH_3), 3.92 (d, 1) and 6.0 (d,1) (AB-system, J = 12.5 Hz, C_4-H) 4.37 (q, J = 6 Hz, 2, OCH_2), 6.7-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{21}H_{17}ClFN_3O_2$: C, 63.40; H, 4.31; N, 10.56. Found: C, 63.42; H, 4.26; N, 10.60.

B. Phosphorus trichloride, 1 ml was added to a solution of 1 g of **33** in 25 ml of methylene chloride. After standing at room temperature for two days, the solution was washed with 10% aqueous sodium carbonate solution, dried and evaporated. Crystallization of the residue from ether gave 0.8 g (83%) of product with mp 174-176°.

C. A mixture of 0.5 g (1.24 mmoles) of **21**, 30 ml of tetrahydrofuran, 10 ml of ethanol and 0.25 g of 10% palladium on carbon was hydrogenated at atmospheric pressure for 3 hours. A solution of acetaldehyde in tetrahydrofuran 10% (v/v) was then added in three 0.2 ml portions at 1 hour intervals. After a total reaction time of 6 hours the catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed over 7 g of silica gel using methylene chloride/ethyl acetate 1:1. Crystallization of the clean fractions from ether gave 80 mg (16%) of product which was recrystallized from ethyl acetate/hexane to show mp 196-198°.

In a similar fashion as described under A. were obtained:

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Isopropyl Ester (**39**).

This compound, obtained in 58% yield from **27** and in 86% yield from the *N*-oxide, was crystallized from ether and recrystallized from ethyl acetate, mp 200-202°.

Anal. Calcd. for $C_{22}H_{19}ClFN_3O_2$: C, 64.16; H, 4. 64; N, 10.20. Found: C, 64.28; H, 4.74; N, 10.20.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid *t*-Butyl Ester (**40**).

This compound was obtained in 68% yield by hydrogenation of **28** followed by oxidative condensation with acetaldehyde. It was crystallized from methylene chloride/hexane to leave colorless crystals with mp 215-217°.

Anal. Calcd. for $C_{23}H_{21}ClFN_3O_2$. C, 64.86; H, 4.97; N, 9.86. Found: C, 64.96; H, 4.87; N, 9.89.

8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Isopropyl Ester (**41**).

This compound was obtained in 73% yield by reduction of the corresponding *N*-oxide **36** with phosphorus trichloride. It was crystallized from ethyl acetate/hexane and had mp 183-185°.

Anal. Calcd. for $C_{21}H_{17}ClFN_3O_2$: C, 63.40; H, 4.31; N, 10.56. Found: C, 63.24; H, 4.15; N, 10.75.

8-Chloro-6-(2-fluorophenyl)-4-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid *t*-Butyl Ester (**42**).

This compound was prepared in 72% yield by hydrogenation of **28** followed by reaction with dimethylformamide dimethylacetal. It was crystallized from methylene chloride/ether and had mp 209-210°.

Anal. Calcd. for $C_{22}H_{19}ClFN_3O_2$: C, 64.16; H, 4.65; N, 10.20. Found: C, 64.13; H, 4.58; N, 10.07.

8-Chloro-6-(2-fluorophenyl)-*N*,*N*-dimethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (**43**).

A mixture of 230 mg (0.6 mmole) of **29**, 20 ml of tetrahydrofuran, 10 ml of ethanol, 0.5 g of Raney nickel and three drops of methanolic ammonia was hydrogenated at atmospheric pressure for 5 hours. The catalyst was separated and the orange colored filtrate was evaporated. The residue was dissolved in ethyl acetate and treated with 0.2 ml of dimethylformamide dimethylacetal. After heating this solution to reflux for 5 minutes, it was evaporated and the residue was chromatographed over 7 g of silica gel using 5% (v/v) of ethanol in methylene chloride. Crystallization of the combined clean fractions from ether gave 80 mg (35%) of product with mp 210-215°. The analytical sample was recrystallized from ether and had mp 216-217°; nmr (deuteriochloroform): 3.24 (broad s, 6, NMe_2), the C_4-protons appear as very broad signal between 4 and 6 ppm, 6.7-7.8 (m, 7, aromatic H), 7.8 (s, 1, C_1-H).

Anal. Calcd. for $C_{20}H_{16}ClFN_4O$: C, 62.75; H, 4.21; N, 14.69. Found: C, 62.67; H, 4.29; N, 14.50.

8-Chloro-6-(2-fluorophenyl)-1-(ethoxycarbonyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-3-carboxylic Acid *t*-Butyl Ester (**44**).

A mixture of 20 g (48 mmoles) of **28**, 200 ml of tetrahydrofuran, 100 ml of methanol, 20 g of Raney nickel and 10 ml of methanolic ammonia 20% (v/v) was hydrogenated at atmospheric pressure for 4 hours. The residue obtained after the usual workup was dissolved in 300 ml of methylene chloride and treated with 12 g of ethyl glyoxalate. After stirring this mixture in an open flask for 24 hours it was evaporated and the residue was crystallized from ether to yield 12.5 g (53%) of product which was recrystallized from ethanol/ether for analysis, mp 195-196°; nmr (deteriochloroform): 1.38 (t, J = 6.5 Hz, 3, CH_3), 1.65 (s, 9, CMe_3), 3.97 (d, 1) and 6.11 (d, 1) (AB-system, J = 12.5 Hz, C_4-H), 4.43 (q, J = 6.5 Hz, 2, OCH_2), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{25}H_{23}ClFN_3O_4$: C, 62.05; H, 4.79; N, 8.69. Found: C, 62.18; H, 4.84; N, 8.53.

2-{[(Dimethylamino)methyl]imino}[7-chloro-5-(2-fluorophenyl)-1,2,3,4-tetrahydro-2*H*-1,4-benzodiazepin-2-ylidene]acetonitrile (**45**).

A solution of 0.34 g (1.2 mmoles) of **30** in 20 ml of acetic acid and 25 ml of methylene chloride was treated with 0.34 g of zinc dust and stirred for 2 hours. The mixture was filtered and the filtrate was diluted with 100 ml of water and 100 ml of methylene chloride and was made alkaline with ammonia. The methylene chloride layer was dried and evaporated. The residue was dissolved in 50 ml of ethyl acetate and reacted with 0.16 ml (1.2 mmoles) of dimethylformamide dimethylacetal and then heated to reflux for 5 minutes. After dilution with 25 ml of hexane the reaction mixture was cooled and the separated crystals were collected and washed with ether to yield 0.22 g (48%) of product with mp 215-218°. For analysis it was recrystallized from methylene chloride/ethyl acetate.

Anal. Calcd. for $C_{20}H_{19}ClFN_5$: C, 62.58; H, 4.98; N, 18.24. Found: C, 62.41; H, 4.83; N, 18.11.

8-Chloro-6-(2-fluorophenyl)-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carbonitrile (**46a**).

A solution of 5.3 g (13.8 mmoles) of **45** in 40 ml of acetic acid was heated to reflux for 5 minutes with stirring. After dilution with water the product was extracted with methylene chloride. The extracts were dried and evaporated and the residue was crystallized from ethyl acetate/hexane to yield a first crop of 2.4 g with mp 163-166°. The mother liquor was poured over a pad of silica gel using 10% (v/v) of ethyl acetate in

methylene chloride. The fractions containing products were combined and evaporated and crystallized from ethyl acetate/hexane to leave another 1.7 g of crystals for a total yield of 4.1 g or 88%. The analytical sample was recrystallized from the same solvents and had mp 165-168°; nmr (deuteriochloroform): 2.46 (broad s, 1, NH), 3.7 (broad d, 1) and 4.33 (broad d, 1) (AB-system, J = 15 Hz, C_4-H), 5. 2 (s, 1, C_6-H), 6.8-8.0 (m, 8, aromatic H).

Anal. Calcd. for $C_{18}H_{12}ClFN_4$: C, 63.28; H, 3.57; N, 16.54. Found: C, 63.85; H, 3.70; N, 16.81.

8-Chloro-6-(2-chlorophenyl)-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carbonitrile .0.66 Molar Ethanol Solvate (**46b**).

A solution of 3 g (8.5 mmoles) of **47** in 25 ml of acetic acid and 25 ml of methylene chloride was treated with 3 g of zinc dust and stirred for 2 hours at room temperature. The zinc was filtered off and the filtrate was diluted with water, basified with ammonia and extracted with methylene chloride. The extracts were dried and evaporated. The residue was crystallized from tetrahydrofuran/ethanol to yield 2.8 g (86%) of product with mp 130-133°; nmr and analytical data indicated the incorporation of 0.66 mole of ethanol.

Anal. Calcd. for $C_{18}H_{12}Cl_2N_4$ .0.66 C_2H_6O: C, 60.14; H, 4.10; N, 14.53. Found: C, 60.17; H, 4.43; N, 14.56.

8-Chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carbonitrile (**47**).

A mixture of 4.5 g (12 moles) of **48b** [5], 13.5 g of phosphorus pentoxide and 200 ml of pyridine was heated to reflux with stirring for 30 minutes. The liquid was decanted and evaporated under reduced pressure and then recombined with the resinous residue which was treated with methylene chloride, ice and 10% aqueous sodium carbonate solution. The orgainic phase was separated, dried and evaporated. Crystallization of the residue from ethyl acetate/hexane gave 3.6 g (82%) of crude product which was recrystallized from the same solvents for analysis, mp 215-217°; nmr (deuteriochloroform): 4.86 (broad s, 2, C_4-H), 7.1-7.7 (m, 7, aromatic H), 8.13 (s, 1, C_1-H).

Anal. Calcd. for $C_{18}H_{10}Cl_2N_4$: C, 61.20; H, 2.85; N, 15.86. Found: C, 61.46; H, 2.97; N, 16.16.

8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (**48a**).

A solution of 200 mg (0.59 mmole) of **46a** in 40 ml of 1,2-dichloroethane was treated with 1 g of activated manganese dioxide and heated to reflux with stirring for 2 hours. The manganese dioxide was filtered off and the filtrate was evaporated. The crystalline product was collected and washed with ether to give 120 mg (57%) of product with mp 302-305°. It was identical in every respect with a sample prepared from the ester 42 *via* the corresponding acid. The analytical sample was recrystallized from tetrahydrofuran/ethanol.

Anal. Calcd. for $C_{18}H_{12}ClFN_4O$: C, 60.94; H, 3.41; N, 15.79. Found: C, 61.16; H, 3.50; N, 15.87.

8-Chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepie-3-carboxamide (**48b**) [5].

A solution of 0.1 g (0.28 mmole) of **47** in 1 ml of concentrated sulfuric acid was allowed to stand at room temperature for 1.5 hours and was then poured on ice. This mixture was stirred and made alkaline by addition of ammonia. The crystalline product was filtered off, washed with water and sucked dry. After drying overnight at 100° under vacuum, 92 mg (88%) of product with mp 325-328° was obtained, identical in every respect with a previously prepared sample [5].

8-Chloro-6-(2-chlorophenyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carbonitrile (**49**).

A mixture of 1 g (2.6 mmoles) of **46b**, 1 ml of diethyl azodicarboxylate and 50 ml of toluene was heated to reflux for 24 hours. The solvent was evaporated and the residue was chromatographed over 30 g of silica gel using 10% (v/v) of ethyl acetate in methylene chloride. The less polar product was crystallized from ethyl acetate to yield 0.45 g (49%) of colorless crystals with mp 257-259°; nmr (deuteriochloroform): 5.6 (d, 1, J = 2 Hz, C_6-H), 6.66 (s with fine structure, 1, C_7-H), 7.2-8.4 (m, 7, aromatic H), 8.65 (d, J = 2 Hz, 1, C_4-H).

Anal. Calcd. for $C_{18}H_{10}Cl_2N_4$: C, 61.21; H, 2.85; N, 15.86. Found: C, 60.94; H, 2.99; N, 15.87.

The fractions containing the more polar component were combined and evaporated. Crystallization from ethyl acetate/hexane gave 0.3 g (33%) of compound **47** with mp 214-216°.

8-Chloro-6-(2-chlorophenyl)-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxamide (**50**).

A. A solution of 0.1 g (0.26 mmoles) of **46b** in 2 ml of concentrated sulfuric acid was allowed to sit at room temperature for 3 hours. After pouring into ice-water, the solution was made alkaline by addition of ammonia. The precipitated product was collected, sucked dry and recrystallized from methylene chloride/ethanol to give 80 mg (83%) with mp > 320°. The analytical sample was recrystallized from dimethylformamide.

Anal. Calcd. for $C_{18}H_{14}Cl_2N_4O$: C, 57.92; H, 3.78; N, 15.01. Found: C, 58.02; H, 3.72; N, 14.86.

B. A mixture of 3.7 g (10 mmoles) of **48b** [5], 50 ml of acetic acid, 50 ml of methylene chloride and 3.7 g of zinc dust was stirred at room temperature for 1 hour. The zinc was separated by filtration and the filtrate was diluted with methylene chloride/ethanol and treated with dilute ammonia. The insoluble product was filtered off, dissolved in methylene chloride/methanol and the solution was combined with the methylene chloride/ethanol extract. The crude product obtained by evaporation was recrystallized from boiling dimethylformamide to yield 2.7 g (73%) of **50**.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*alpha*-(hydroxyimino)-1*H*-1,4-benzodiazepine-2-acetic Acid *t*-Butyl Ester (**51**).

Sodium borohydride, 12 g, was added in two portions within 2 hours to a solution of 20 g (48 mmoles) of **28** in 800 ml of ethanol and 400 ml of methylene chloride. After heating to reflux for 5 hours, the reaction mixture was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was dried and evaporated. The residue was chromatographed over 400 g of silica gel using methylene chloride/ethyl acetate 7:3 (v/v) for elution. Crystallization of the combined clean fractions from methylene chloride/ether/hexane yielded 7.5 g (37%) of light yellow product which was recrystallized from ethyl acetate for analysis, mp 203-204° dec; uv: max 226 nm (26000), sh 244 (24000), max 372 (3000); nmr (deuteriochloroform + d-DMSO): 1.43 (s, 9, CMe_3), 4.13 (m, 2, C_3-H), 5.37 (m, 1, C_2-H) 6.07 (broad s, 1, NH), 6.6-7.6 (m, 7, aromatic H), 12.1 (broad s, 1, OH).

Anal. Calcd. for $C_{21}H_{21}ClFN_3O_3$: C, 60.36; H, 5.07; N, 10.06. Found: C, 60.16; H, 4.86; N, 9.87.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*alpha*-(hydroxyimino)-*N*,*N*-dimethyl-1*H*-1,4-benzodiazepine-2-acetamide (**52**).

A mixture of 10 g (26 mmoles) of **29**, 400 ml of ethanol and 3 g of sodium borohydride was stirred at room temperature for 48 hours. The reaction mixture was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether gave 5 g (50%) of light yellow crystals. The analytical sample was recrystallized from methylene chloride/ethanol and had mp 214-215°; nmr (d-DMSO): 2.76 (s, 3, NMe), 2.8 (s, 3, NMe), 4.05 (m, 2, C_3-H), 4.8 (m, 1, C_2-H), 6.4-7.8 (m, 8, aromatic H and NH), 11.4 (s, 1, OH).

Anal. Calcd. for $C_{19}H_{16}ClFN_4O_2$: C, 58.69; H, 4.67; N, 14.41. Found: C, 58.94; H, 4.71; N, 14.33.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-*N*,*N*-dimethyl-1*H*-1,4-benzodiazepine-2-(*N'-hydroxy*)*iminomethanesulfonamide* (**53**).

A suspension of 3.9 g (9.2 mmoles) of **31** in 85 ml of ethanol was treated with 2 g (52.6 mmoles) of sodium borohydride and stirred for 3 hours. The mixture was diluted with water and saturated sodium bicarbonate solution and stirred for 3 hours. The precipitated product was

filtered off to leave after drying 2.6 g (66%) with mp 194-202° dec. Recrystallization from tetrahydrofuran/ethanol gave yellow crystals with mp 242-244°; nmr (d-DMSO): 2.85 (s, 6, NMe_2), 3.7-4.6 (m, 2, C_3-H) 5.2 (m, 1, C_2-H) 6.5 (broad s, 1, NH), 6.6-7.7 (m, 7, aromatic H).

Anal. Calcd. for $C_{18}H_{16}ClFN_4O_3S$: C, 50.88; H, 4.27; N, 13.19. Found: C, 50.89; H, 4.12; N, 12.95.

[7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepin-2-yl]-2-pyridylmethanone Oxime (**54**).

A mixture of 3.92 g (10 mmoles) of **32**, 200 ml of tetrahydrofuran, 200 ml of ethanol and 3.9 g of sodium borohydride was stirred for 4.5 hours. The mixture was partially evaporated under reduced pressure and partitioned between methylene chloride and sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was crystallized from ether to leave 2.6 g (66%) of product with mp 202-206°. The analytical sample was recrystallized from methanol to give off white crystals with mp 211-213°; nmr (d-DMSO): 3.96 (m, 2, C_3-H), 5.2 (m, 1, C_2-H), 6.6-8.0 (m, 11, aromatic H and NH), 8.65 (m, 1, C_6-H of pyridine), 11.4 (s, 1, OH).

Anal. Calcd. for $C_{21}H_{16}ClFN_4O$: C, 63.88; H, 4.09; N, 14.19. Found: C, 63.69; H, 4.21; N, 14.18.

[7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepin-2-yl]-2-pyridylmethanone *O*-Methyloxime (**55**).

A solution of 8.7 g (22 moles) of **54** in 250 ml of methylene chloride and 125 ml of methanol was treated with an excess of diazomethane in ether and stirred for 1 hour. The excess diazomethane was destroyed by addition of acetic acid and the mixture was diluted with 250 ml of methylene chloride and washed with saturated sodium bicarbonate solution. The organic layer was treated with charcoal, dried and evaporated. The residue was passed over a pad of silica gel using 10% (v/v) of ethyl acetate in methylene chloride. Crystallization of the combined clean fractions from ether/hexane gave 3.2 g (36%) of crystals with mp 171-173°; nmr (deuteriochloroform): 4.02 (s, broad s, 2, C_3-H) 6.7-8.0 (m, 10, aromatic H), 8.65 (m, 1, C_6-H) of pyridine).

Anal. Calcd. for $C_{22}H_{16}ClFN_4O$: C, 64.95; H, 3.96; N, 13.77. Found: C, 64.94; H, 4.14; N, 13.78.

7-Chloro-5-(2-fluorophenyl)-*N*,*N*-dimethyl-3*H*-1,4-benzodiazepine-2-(*N'*-methoxy)iminomethanesulfonamide (**56**) and 7-Chloro-5-(2-fluorophenyl)-*N*,*N*-dimethyl-3*H*-1,4-benzodiazepine-2-(methylimino)methanesulfonamide *N'*-Oxide (**62**).

A suspension of 2.92 g (6.9 mmoles) of **31** in 50 ml of ethanol was treated with an excess of diazomethane in ether, added in portions over a period of 45 minutes. The excess diazomethane was destroyed by addition of acetic acid and the reaction mixture was evaporated. The residue was chromatographed over 100 g of silica gel using 10% (v/v) of ethyl acetate in methylene chloride. The fractions containing the separated products were evaporated. The less polar compound **56** was crystallized from ether to give 1.2 g (40%) with mp 165-168° after recrystallization from ether; nmr (deuteriochloroform): 2.88 (s, 6, NMe_2), 4.0 (s, 3, OMe), 4.13 (s, 2, C_3-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{18}ClFN_4O_3S$: C, 52.24; H, 4.15; N, 12.82. Found: C, 52.53; H, 4.25; N, 12.55.

The more polar compound **62** was crystallized from ether to leave 0.9 g (30%) with mp 173-175° after recrystallization from ether; nmr (deuteriochloroform): 2.67 (s, 6, NMe_2), 4.23 (broad s, 2, C_3-H), 4.28 (s, 3, NMe), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{18}ClFN_4O_3S$: C, 52.24; H, 4.15; N, 12.82. Found: C, 52.26; H, 3.92; N, 12.81.

9-Chloro-7-(2-fluorophenyl)-4a,5-dihydro-1*H*-[1,2,5]oxadiazino[5,4-*a*]-[1,4]benzodiazepine-4-carboxylic Acid *t*-Butyl Ester (**57**).

A mixture of 1.5 g (3.6 mmoles) of **51**, 0.75 g of paraformaldehyde, 100 ml of ethanol and a few crystals of para-toluenesulfonic acid was heated to reflux for 6 hours. After partial evaporation the remaining reaction mixture was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ether to give 0.7 g (45%) of product which was recrystallized from ethanol for analysis and had mp 216-217° dec; nmr (deuteriochloroform): 1.53 (s, 9, CMe_3), 3.3 (dd, 1, J = 11 Hz and J = 12 Hz, C_5-H), 4.56 (dd, 1, J = 11 Hz and J = 4 Hz, C_5-H), 5.22 (dd, 1, J = 12 Hz and J = 4 Hz, C_4a-H), 5.28 (center of AB-system, J = 11 Hz, 2, C_1-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{22}H_{21}ClFN_3O_3$: C, 61.47; H, 4.92; N, 9.78. Found: C, 61.53; H, 4.69; N, 9.48.

9-Chloro-7-(2-fluorophenyl)-4a,5-dihydro-*N*,*N*-dimethyl-1*H*-[1,2,5]-oxadiazino[5,4-*a*][1,4]benzodiazepine-4-carboxamide (**58**).

A mixture of 3 g (7.7 mmoles) of **52**, 0.75 g of paraformaldehyde, 2 g of pivalic acid and 200 ml of 1,2-dichloroethane was heated to reflux for 1.5 hours. The solution was washed with 10% aqueous sodium carbonate solution, dried and evaporated. Crystallization of the residue from ethyl acetate/ether gave 3 g (96%) of product which was recrystallized from 2-propanol for analysis, mp 177-179°; nmr (deuteriochloroform + 2 drops of d-DMSO): 3.06 and 3.1 (2s, 6, NMe_2), 3.76 (dd, 1, J = 12 Hz, J = 6 Hz, C_5-H), 4.65 (dd, 1, J = 12 Hz, J = 1.5 Hz, C_5-H), 5.0-5.6 (m, 3, C_1-H, C_4a-H), 6.7 (d, 1, J = 9 Hz, C_{11}-H), 6.9-7.8 (m, 6, aromatic H).

Anal. Calcd. for $C_{20}H_{18}ClFN_4O_2$: C, 59.93; H, 4.53; N, 13.98. Found: C, 60.00; H, 4.60; N, 14.11.

9-Chloro-7-(2-fluorophenyl)4a,5-dihydro-*N*,*N*-dimethyl-1*H*-[1,2,5]oxadiazino[5,4-*a*][1,4]benzodiazepine-4-sulfonamide (**59**).

A solution of 1.7 g (4 mmoles) of **53** in 250 ml of toluene was treated with 0.36 g (12 mmoles) of paraformaldehyde and 1.7 g of pivalic acid and heated to reflux with separation of water for 3 hours. It was then washed with saturated sodium bicarbonate solution, dried and evaporated. The residue was chromatographed over a short column of silica gel using ethyl acetate/methylene chloride 1:1. Crystallization of the clean fractions from methylene chloride/ethyl acetate yielded 0.45 g (26%) of product with mp 240-242° dec; nmr (deuteriochloroform): 3.0 (s, 6, NMe_2), 3.45 (t, J = 11.5 Hz, 1, C_5-H), 4.78 (dd, 1, J = 11 Hz, J = 4 Hz, C_5-H), 5.18 (dd, 1, J = 12 Hz, J = 4 Hz, C_4a-H), 5.35 (center of AB-system, J = 11.5 Hz, 2, C_1-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{18}ClFN_4O_3S$: C, 52.24; H, 4.15; N, 12.82. Found: C, 52.19; H, 4.25; N, 12.58.

9-Chloro-7-(2-fluorophenyl)-4a,5-dihydro-4-(2-pyridyl)-1*H*-[1,2,5]oxadiazino[5,4-*a*][1,4]benzodiazepine (**60**).

A mixture of 4.5 g (11.4 mmoles) of **54**, 1.02 g (34 mmoles) of paraformaldehyde, 4.5 g of pivalic acid and 250 ml of toluene was heated to reflux with separation of water for 3 hours. After evaporation, the residue was partitioned between methylene chloride and sodium bicarbonate solution and the organic phase was dried and evaporated. Crystallization of the residue from ethyl acetate yielded 2.5 g (54%) of product with mp 230-233°. Recrystallization from methylene chloride/ethyl acetate for analysis gave colorless crystals with mp 241-243°; nmr (d-DMSO): 3.73 (dd, 1, J = 12 Hz, J = 6 Hz, C_5-H), 5.1 (m, 2, C_4a-H and C_5-H), 5.78 (narrow AB-system, 2, C_1-H), 6.95 (d, 1, J = 9 Hz, C_{11}-H), 7.0-8.4 (m, aromatic H, 8.55) (m, 1, C_6-H of pyridine), 8.95 (d with fine structure, J = 8 Hz, 1, C_3-H of pyridine).

Anal. Calcd. for $C_{22}H_{16}ClFN_4O$: C, 64.95; H, 3.96; N, 13.77. Found: C, 64.73; H, 3.90; N, 13.90.

9-Chloro-7-(2-fluorophenyl)-4a,5-dihydro-1-methyl-1*H*-[1,2,5]oxadiazino[5,4-*a*][1,4]benzodiazepine-4-carboxylic Acid *t*-Butyl Ester (**61**).

A mixture of 3 g (7.2 mmoles) of **51**, 75 ml of ethanol, 3 ml of acetaldehyde and 5 g of molecular sieves 5A was allowed to stand at room temperature for 3 days. Following the addition of another 5 g of molecular sieves stirring was continued for additional 24 hours. The separated crystals and the molecular sieves were separated and washed with a little ethanol. The crystalline product was separated from the molecular sieves by dissolving in methylene chloride. The solution was evaporated and the residue was crystallized from ether/hexane to give 1 g of colorless crystals with mp 196-197° dec. From the original filtrate additional 0.4 g of product with the same mp was obtained for a total yield

of 1.4 g (44%); nmr (deuteriochloroform): 1.53 (s, 9, CMe_3), 1.6 (d, 3, J = 6 Hz, Me), 3.12 (dd, 1, J = 11 Hz, J = 12 Hz, C_5-H), 4.55 (dd, 1, J = 11 Hz, J = 4 Hz, C_5-H), 5.08 (dd, 1, J = 12 Hz, J = 4 Hz, C_4a-H), 5.37 (q, 1, J = 6 Hz, C_1-H), 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{23}H_{23}ClFN_3O_3$: C, 62.23; H, 5.22; N, 9.47. Found: C, 62.19; H, 5.21; N, 9.19.

8-Chloro-6-(2-fluorophenyl)-3-(2-pyridyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (**63**).

A mixture of 0.5 g (1.23 mmoles) of **55**, 20 ml of ethanol and 0.5 g of sodium borohydride was stirred at room temperature for 6 hours. The reaction mixture was partially evaporated and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated. The yellow residue of crude [7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine-2-yl]-2-pyridylmethanone *O*-methyloxime was dissolved in 12 ml of glacial acetic acid. The solution was treated with 0.25 g of paraformaldehyde and heated on the steam bath for 10 minutes. After evaporation of the solvent, the residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic layer was dried and evaporated. The residue was chromatographed over 8 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The fractions containing product were combined, evaporated and crystallized from ethyl acetate/ether to give 80 mg (17%) of crystals. The analytical sample was recrystallized from the same solvents to give colorless product with mp 199-201°; uv: max 217 nm (38000) 247 (29100) sh 259 (26700) 292 (18600); nmr (deuteriochloroform): C_4-protons appear as very broad signals at *ca.* 4.2 and 6.3 ppm, 6.7-8.2 (m, 10 aromatic H), 7.98 (s, 1, C_1-H), 8.65 (m, 1, C_6-H of pyridine).

Anal. Calcd. for $C_{22}H_{14}ClFN_4$: C, 67.96; H, 3.63; N, 14.41. Found: C, 68.06; H, 3.48; N, 14.47.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-(2-pyridyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (**64**).

Reduction of 0.7 g of **55** with sodium borohydride as described above gave 0.5 g of crude dihydro derivative which was heated to reflux in 20 ml of glacial acetic acid containing 0.5 ml of acetaldehyde for 15 minutes. The usual workup followed by chromatography over 5 g of silica gel using methylene chloride/ethyl acetate 1:1 (v/v) and crystallization from ether yielded 0.1 g (14%) of product with mp 245-248°; nmr (deuteriochloroform): 2.55 (s, 3, Me), 4.0 (d, 1) and 6.35 (d, 1) (AB-system, J = 12.5 Hz, C_4-H), 6.7-8.0 (m, 10, aromatic H), 8.43 (m, 1, C_6-H of pyridine).

Anal. Calcd. for $C_{23}H_{16}ClFN_4$: C, 68.57; H, 4.00; N, 13.90. Found: C, 68.24; H, 3.85; N, 13.95.

8-Chloro-6-(2-fluorophenyl)-*N*,*N*-dimethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-sulfonamide (**65**) and *N*-Acetoxy-7-chloro-5-(2-fluorophenyl)-*N*-methyl-3*H*-1,4-benzodiazepine-2-carboxamide (**67**).

A solution of 425 mg (0.97 mmole) of **62** in 20 ml of acetic anhydride was heated to reflux for 20 minutes. The reagent was evaporated and the residue was chromatographed over 10 g of silica gel using ether/toluene 3:7. The less polar component **67** was crystallized from ether to leave 48 mg (13%) with mp 145-148° after recrystallization from ether/hexane; ir (chloroform): 1800 cm^{-1} (N-OAc), 1667 (CO); nmr (deuteriochloroform): 1.93 (s, 3, Ac), 3.42 (s, 3, NMe), 4.25 (s, 2, C_3-H) 6.8-7.8 (m, 7, aromatic H).

Anal. Calcd. for $C_{19}H_{15}ClFN_3O_3$: C, 58.85; H, 3.90; N, 10.84. Found: C, 58.73; H, 3.74; N, 10.83.

The more polar **65** was crystallized from ethyl acetate/hexane to yield 95 mg (23%) of crystals with mp 178-180°; nmr (deuteriochloroform): 2.9 (s, 6, NMe_2), *ca.* 4.2 (very broad s) and *ca.* 5.7 (very broad s) (AB-system of C_4-H), 6.8-7.9 (m, 7, aromatic), 8.03 (s, 1, C_1-H).

Anal. Calcd. for $C_{19}H_{16}ClFN_4O_2S$: C, 54.48; H, 3.85; N, 13,38. Found: C, 54.41; H, 3.94; N, 13.38.

Acknowledgment.

The authors wish to thank Dr. F. Scheidl for the microanalyses and Dr. V. Toome for the uv and ir spectra. We are grateful to Mrs. M. Satchwell for the typing of the manuscript.

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