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3-FLUOROBENZODIAZEPINES

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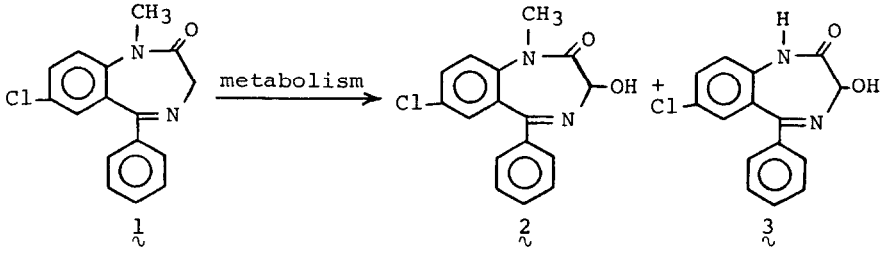
SUMMARY

Benzodiazepines that bear a fluorine substituent in the metabolically active C-3 position were prepared by the reaction of diethylaminosulfur trifluoride (DAST) with the corresponding 3-hydroxybenzodiazepines. These products are surprisingly stable to hydrolysis and possess potent antianxiety and muscle-relaxing properties.

INTRODUCTION

Diazepam (Valium®), 1, is metabolized in man by hydroxylation at the 3-position (also with some N-demethylation) to give 3-hydroxybenzodiazepines 2 and 3 [1]. Related pharmaceutically active benzodiazepines are also metabolized in a similar manner. These 3-hydroxy metabolites are also pharmaceutically active, but their activity is of very short duration for they are rapidly excreted as glucuronides.



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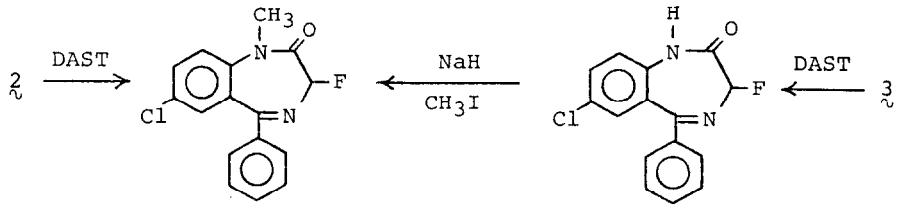
Substitutions of a fluorine for a hydrogen at the 3-position in the benzodiazepine ring would be expected to inhibit this metabolic pathway, and thus could increase the residence time of the unmetabolized compound and, therefore, its potency or duration of action. To evaluate the effect of a fluorine substituent at this position, a number of 3-fluorobenzodiazepines were prepared.

RESULTS AND DISCUSSION

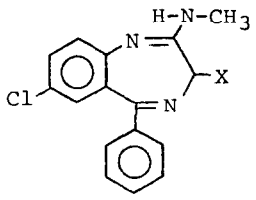
Preparation of 3-fluorodiazepines

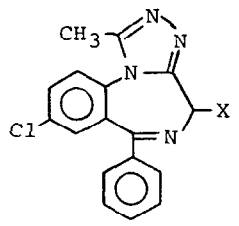
3-Hydroxydiazepam (2) and 3-hydroxy-N-desmethyldiazepam (3) both react with diethylaminosulfur trifluoride (DAST) [2] under mild conditions to give high yields of the corresponding 3-fluoroderivatives (4 and 5). With 3 and with other benzodiazepinones that have an unsubstituted nitrogen at the 1-position, the fluorination reaction must be conducted at low temperature and quenched immediately with water after warming no higher than -10° to prevent DAST and by-product Et_2N-SOF from reacting with the NH function.



4 5

Several other 3-fluorobenzodiazepinones (6-13) were prepared by similar procedures and are listed in Table I. In addition, an isomeric derivative of chlordiazepoxide (Librium®), 14, and a pharmaceutically active triazolobenzodiazepine, 16 [3], were also converted to the corresponding fluoro-derivatives (15 and 17) by treatment with DAST.





14, X = OH

15, X = F

16, X = OH

17, X = F

The 3-fluorobenzodiazepinones unsubstituted at the 1-nitrogen could be N-alkylated or N-acylated by standard techniques. For example, 5 reacts with sodium hydride and methyl iodide in tetrahydrofuran to give 4, and with methyl or ethyl isocyanate to give the ureas 25 and 27. Several other 1-alkyl-3-fluorobenzodiazepinones (18-24), listed in Table I, were prepared by similar alkylation procedures.

Properties of 3-fluorobenzodiazepinones

Most of the 3-fluorobenzodiazepinones prepared in this study are white crystalline compounds that are surprisingly resistant to solvolysis. For example, 3-fluorodiazepam (5) can be recrystallized from hot ethanol and is unreactive to pyridine. This is in marked contrast to 3-chlorodiazepam, which reacts vigorously with cold ethanol and pyridine. [4] The hydrogen in the 3-position, geminal to the fluorine, is relatively acidic, as evidenced by a rapid base-catalyzed exchange with deuterium oxide.

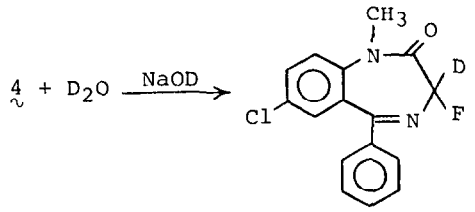
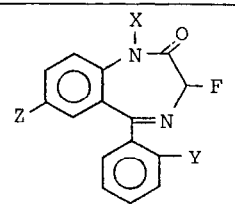


TABLE I

3-Fluorobenzodiazepines (nc)



Compound No.	Structure X	Y	Z	Procedure(s)	Yield[g]	mp°C	Anal.[f]	^{1}H NMR;δ,ppm	^{19}F NMR;δ,ppm[e]
4	CH_3	H	Cl	B C	90% 50%	138-140°	C,H,N,F	($CDCl_3$)3.43 (s,3H); 5.54 (d,J=57Hz,1H); 7.5 (m,8H)	-161.7 (d,J=57Hz)
5	H	H	Cl	A	82%	190-192°	C,H,N	(DMSO-d_6)7.2-7.8 (m,8H); 5.72 (d, J=56Hz,1H);11.0(1H)	-161.5 (d,d; J=56,4Hz)
6	H	F	Cl	A	98%	206-207°	C,H,N,F	(DMSO-d_6) 5.95 (d, J=56Hz,1H); 7.47(m, 7H);11.25(s,1H)	-162.0 (d,J=56Hz, 1F); -113.0 (m,1F)
7	C_2H_5	H	Cl	B	90%	156-158°	C,H,N,F	(DMSO-d_6) 7.2-7.8 (m,8H); 5.85 (d,J= 57Hz,1H);3.5-4.38 (m,2H);1.02(t,3H)	
8	CH_3	F	Cl	B	83%	91-95°	C,H,N,F	($CDCl_3$) 3.5 (s,3H); 5.66 (d,J=57Hz,1H); 7.5 (m,7H)	-162.4 (d,J=57Hz, 1F) -111.9 (m,1F)

9	H	H	Br	A	88%	207-209° (dec.)	C,H,N,F	($(CD_3)_2CO$) 5.86 (d, J=57Hz,1H); 7.2-8 (m,8H); 9.90 (NH)	-162.6 (d,J=57Hz)
10	H	F	Br	A	74%	195-197° (dec.)	C,H,N,F	(DMSO-d_6) 5.88 (d, J=56Hz,1H); 7.2-7.9(m,7H),11.2 (NH)	-162.1(d,J=56Hz, 1F); -113.0 (m,1F)
11	H	Cl	Cl	A[c]	53%	210-211°		(DMSO-d_6)11.3 (m, 1H);7.2 (m,6H);7.03 (d,1H);5.92(d,J= 56Hz,1H)	-162.3(d,dJ-56, 4Hz)
12	H	H	NO_2	A	83%	174-175° (dec.)	C,H,N,F	(DMSO-d_6)5.9(d,J= 57Hz,1H);7.3-7.7 (m,6H);8.07(d,J= 2.5Hz,1H);8.45 (d, d,J=9.0,2.5Hz,1H)	-161.4(d,J=57Hz)
13	H	H	H	A	88%	156-158° (dec.)	C,H,N,F	(DMSO-d_6)5.75(d,J= 57Hz,1H);7.5(m,8H)	-161.4(d,J=57Hz)
15	-----a-----			A[d]	82%	232-235°		(DMSO-d_6)7.3-8.1 (m,8H);6.71(d,J= 52Hz,1H);2.62(s,3H)	-167.1(d,J=52Hz)
17	-----b-----			A	85%	139-141°	C,H,F,N	($CDCl_3$)2.96(d,J= 5Hz,3H),5.41(d, J=58Hz,1H),5.86 (1H),7.1-7.8(m,8H)	-159.4(d,d,J=58, 2.5Hz)

(continued overleaf)

TABLE I (cont.)

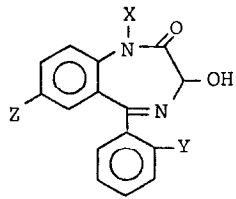
Compound No.	Structure X	Y	Z	Procedure(s)	Yield[g]	mp°C	Anal.[f]	^{1}H NMR;δ,ppm	^{19}F NMR;δ,ppm[e]
18	CH_3	H	Br	C[m]	38%	h	C,H,F	($CDCl_3$)3.46 (s,3H); 5.60 (d,J=57Hz,1H); 7.2-7.9 (m,8H)	-161.7 (d,J=57Hz)
20	CH_3	Cl	Cl	C	65%	204-205°	C,H,N, Cl,F	(DMSO-d_6)7.6(m,6H); 7.0(m,1H); 5.94 (d, J=56Hz,14);3.45(s,3H)	-161.8(d,J=56Hz)
21	CH_3	F	Br	A C	92% 50%	127-130°	C,H,N,F	($CDCl_3$)3.49(s,3H); 5.62 (d,J=57Hz,1H); 6.9-7.9(m,7H)	-162.4 (d,J=57Hz, 1F); -111.9 (m,1F)
22	CH_3	H	NO_2	C[i]	60%	i		($CDCl_3$)3.53(s,3H); (d,J=57Hz,1H);7.2-7.9(m,6H);8.2-8.9 (m,2H)	-161.7(d,J=57Hz)
23	CH_3	H	H	C	53%	177-179°	C,H,N,F	($CDCl_3$)3.49(s,3H), 5.68(d,J=57Hz,1H, 7.2-7.9(m,9H)	-161.8(d,J=57Hz)
24	$CH_2CH=CH_2$	H	Cl	C[e]	64%	138-140°	C,H,N,F	($CDCl_3$)7.2-7.9(m, 8H),5.6(d,J=57.5Hz, 1H);4.85-5.95(m,3H); 4.58(2H)	-161.9(d,J=57.5Hz)
25	$CONHCH_3$	H	Cl	D	56%	224-225°	C,H,N,F	($CDCl_3$)8.4-8.7(q broad,1H);7.25-8.0(m,8H);5.72(d, J=57Hz,1H);2.93(d, J=4.5Hz,3H)	-160.75(d,J=57Hz)

26	$CONHCH_3$	F	Cl	D	85%	147-149°	C,H,N	($CDCl_3$)2.90(d,J=5Hz, 3H),5.66(d,J=56Hz, 1H),6.8-8.0(m,7H), 8.6(NH)	-110.1 (m,1F) -161.2 (d,J=57, 1F)
27	$CONHC_2H_5$	H	Cl	D[j]	54%	110-112°		($CDCl_3$)8.7(N-H);7.2-8.0(m,8H);5.67(d,J=57Hz,1H);3.39(d,q,2H);1.2(t,J=7Hz,3H)	-160.67(d,J=57Hz)

(a) 4-Fluoro-8-chloro-1-methyl-6-phenyl-4H-5-triazolo[4.3.a]-[1,4]benzodiazepine, $C_{17}H_{12}ClFN_4$. (b) 3-Fluoro-7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine, $C_{16}H_{13}ClFN_3$. (c) Recrystallized from benzene. (d) The reaction mixture was allowed to warm to -20° and maintained there for 20 min. During work-up, the aqueous mixture was neutralized with sodium bicarbonate. (e) The solvent is the same as that for ^1H NMR. $CFCl_3$ was used as an internal standard. Downfield shifts are reported as positive values. (f) Where analyses are indicated by symbols of the elements, results do not deviate more than ±0.4%. (h) Recrystallization from cyclohexane gave an amorphous cream-colored solid of indistinct melting point. (i) To purify, the residue was dissolved in hot benzene and fractionally precipitated by addition of hexane. The first dark fractions of solids were discarded. Product was obtained as an amorphous tan solid of indictinct melting point. (j) Recrystallized from cyclohexane. (k) Stirred 2 hrs. (l) Alkylated with xs. 3-Bromopropene and stirred 2 hrs. (m) Stirred 2.5 hrs. Recrystallized from cyclohexane.

TABLE II

3-Hydroxybenzodiazepine Intermediates (Trifluoroacetic Anhydride Procedure)

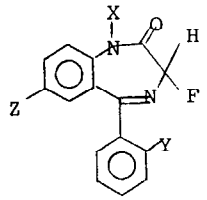


Compound No.	X	Y	Z	Formula	Yield %	Recryst. Solvent	Mp	Analysis[a]
2	CH_3	H	Cl	$C_{16}H_{13}ClN_2O_2$	93	cyclohexane	123-125	Ref 4[b]
3	H	H	Cl	$C_{15}H_{11}ClN_2O_2$	95	EtOH	205-6	Ref 4[b]
30a	H	H	NO_2	$C_{15}H_{11}N_3O_4$	87	EtOH	200-1	Ref 6[b]
30b	H	F	Br(nc)	$C_{15}H_{10}BrFN_2O_2$	62	EtOH	196-8	C,H,F,N
30c	CH_3	F	Br(nc)	$C_{16}H_{12}BrFN_2O_2$	70	chlorobutane	167-9	C,H,N
30d	H	H	Br	$C_{15}H_{11}BrN_2O_2$	85	EtOH	190-2	C,H,N,Ref 8[b]
30e	H	F	Cl(nc)	$C_{15}H_{10}ClFN_2O_2$	92	EtOH	173-5	C,H,N
30f	CH_3	F	Cl(nc)	$C_{16}H_{12}ClFN_2O_2$	90	cyclohexane	162-4	C,H,N
30g	H	Cl	Cl	$C_{15}H_{10}Cl_2N_2O_2$	87	EtOH	166-8	Ref 7[b]
30h	H	H	H (nc)	$C_{15}H_{12}N_2O_2$	71	EtOH	189-91	C,H,N

(a) Where analyses are indicated by symbols of the elements, results do not deviate more than $\pm$ 0.4%. (b) Previously prepared by the method described in this reference.

TABLE III

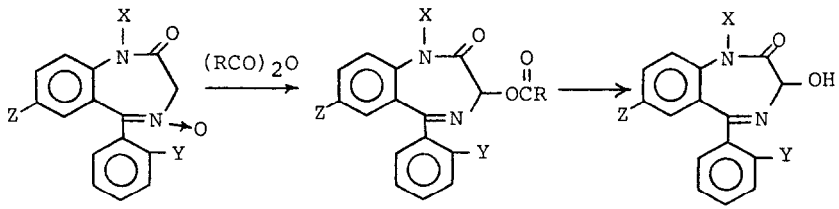
Pharmacology of 3-Fluorobenzodiazepines



Compound	X	Y	Z	Mouse Oral ED50-Mg/Kg (Conf. Limits; α=.05) Antipentylenetetrazole	Anti Straub Tail
Diazepam	H	H	Cl	1.4(0.8;2.5)	0.25(0.14;0.44)
4	CH_3	H	Cl	0.25(0.19;0.34)	0.10(0.05;0.20)
5	H	H	Cl	0.53	0.43
6	H	F	Cl	0.45	0.07
7	C_2H_5	H	Cl	0.56	-
8	CH_3	F	Cl	0.11	-
9	H	H	Br	0.74	-
10	H	F	Br	0.12	-
11	H	Cl	Cl	0.30	0.11
12	H	H	NO_2	0.89	0.60
13	H	H	H	71.	-
18	CH_3	H	Br	0.19	0.08
20	CH_3	Cl	Cl	0.25	0.06
21	CH_3	F	Br	0.07	0.029
22	CH_3	H	NO_2	0.27	0.21
24	CH_2-CH=CH_2	H	Cl	6.1	-
25	$CONHCH_3$	H	Cl	1.2	0.45
26	$CONHCH_3$	F	Cl	0.40	-
27	$CONHC_2H_5$	H	Cl	0.65	0.25

Preparation of 3-hydroxybenzodiazepines

The 3-hydroxybenzodiazepine precursors to the 3-fluorobenzodiazepines were prepared by a modification of a method described by Bell and Childress [4], who treated the 4-oxide 28 (Z=Cl, X=CH_3, Y=H) with acetic anhydride to obtain the 3-acetate (29, R=CH_3, X=CH_3, Y=H, Z=Cl), and then hydrolyzed the acetate to obtain 2. The acetylation reaction goes well, but the hydrolysis step gives low yields because the 3-hydroxy product is unstable to the strongly basic conditions necessary for hydrolysis. We have found that the use of trifluoroacetic anhydride in place of acetic anhydride overcomes this problem. Trifluoroacetic anhydride reacts under very mild conditions (25°) to give high yields of the trifluoroacetate (29, R=CF_3), which can be hydrolyzed under very mild conditions to the 3-hydroxy compound (30) by aqueous-alcoholic sodium bicarbonate at 25°. The 3-hydroxy compounds prepared in this manner are listed in Table II.



28 29 30

Pharmacology

Methods and results

Biological activity for the compounds was shown by their effects orally in the mouse antipentylene tetrazole test used as a paradigm for antianxiety effects in man, and in the mouse Anti Straub tail test used to estimate skeletal muscle relaxant activity.

In the mouse antipentylene tetrazole test, mice were dosed orally with test drug, then at an appropriate time later, usually 30 minutes, were injected intravenously with a normal

saline solution of pentylene tetrazole (Metrazal®) at 40 mg/kg, a dose sufficient to produce clonic convulsions in 98% of mice in 3-10 seconds. All antianxiety drugs block this response. In this test, 3-fluorodiazepam (4) had an Ed50=0.25 mg/kg, and was significantly more potent than diazepam (1) with ED50=1.4 mg/kg. The most potent compound was 21 (Table III), with ED50= 0.07 or about 20 times as potent as diazepam.

In the mouse Anti Straub tail test, mice were dosed orally, then 10 minutes later were challenged with an aqueous solution of morphine sulfate subcutaneously at 40 mg/kg, which typically causes the Straub tail phenomenon [11] in mice. Prevention of the Straub tail erection for 20 minutes was used to estimate skeletal muscle relaxant activity. The most potent muscle relaxant compound also was 21, ED50=0.029 mg/kg and it was 9 times as potent as diazepam (1), ED50=0.25 mg/kg.

EXPERIMENTAL

Proton NMR spectra were obtained on a Varian A-60 instrument with TMS as an internal standard. Fluorine NMR spectra were obtained on a Varian XL-100 instrument operated at 94.1 MHz using $CFCl_3$ as an internal standard. Lower field shifts are reported as positive values.

Procedure A. 3-Fluoro-1,3-dihydro-7-chloro-5-phenyl-2H-14-benzodiazepin-2-one (5) [5]

This procedure illustrates the fluorination of N-unsubstituted benzodiazepinones. Deviations of detail in the syntheses of analogous products are found in Table I.

A well-stirred suspension of 10 g (0.03 mol) of 3-hydroxy-1,3-dihydro-7-chloro-5-phenyl-2H-1,4-benzodiazepin-2-one (3) and 500 ml of methylene chloride was cooled to -70°. Diethylaminosulfur trifluoride (DAST) (25 ml, 0.2 mol) was then added dropwise with exclusion of moisture and air. On completion of the addition, the dry-ice acetone bath was removed, the contents of the flask were allowed to warm up in about 25 minutes to

-10°, and the reaction quenched immediately by pouring into a beaker containing 400-500 ml of ice water. Reaction temperature is an important factor. If the reaction mixture is allowed to warm to 25°, a complex mixture in which 1 is only a minor component is obtained. Vigorous stirring of the ice-water mixture continued for 7 to 10 min. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to give a pale orange powder. The product was dissolved in hot benzene, treated with decolorizing charcoal, and filtered hot. On addition of heptane to the benzene solution and cooling in ice, 8.19 g (82%) of 5 was obtained as a white powder. Spectral and analytical data are in Table I.

Procedure B. 3-Fluoro-1,3-dihydro-1-methyl-7-chloro-5-phenyl-2H-1,4-benzodiazepin-2-one (4)

This procedure illustrates the fluorination of N-alkyl benzodiazepinones. Deviations of detail in the syntheses of analogous products are found in Table I.

A solution of 12.1 g (0.04 mol) of 3-hydroxy-1,3-dihydro-1-methyl-7-chloro-5-phenyl-2H-1,4-benzodiazepin-2-one (3) in 25 ml of anhydrous methylene chloride was added dropwise over a period of 15 min to a stirred solution of 12.6 ml (0.1 mol) of DAST in 300 ml of anhydrous methylene chloride cooled to -70°. The reaction mixture was allowed to warm slowly over a period of 45 min to 5° and then poured into 500 ml of ice and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to give 10.9 g (90%) of crude product as a light yellow solid residue. Recrystallization from heptane gave 8.48 g (70%) of 4 as colorless crystals. Spectral and analytical data are as listed in Table I.

Procedure C. 3-Fluoro-7-bromo-5-(2-fluorophenyl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one (21)

This procedure illustrates the N-alkylation of 3-fluorobenzodiazepinones. Deviations of detail in the syntheses of analogous products are found in Table I.

A slurry of 0.17 g (0.007 mole) of sodium hydride in 10 ml of tetrahydrofuran was added to a solution of 1.8 g (0.005 mole) of 10 and 10 ml methyl iodide in 100 ml tetrahydrofuran. The reaction mixture was stirred for 3 hr at 25° and then poured into 300 ml ice water. The aqueous mixture was extracted with methylene chloride, and the extracts were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. The residue was recrystallized from heptane to give 0.91 g (50%) of 21 as cream-colored crystals: mp 127-130°. Spectral and analytical data are as listed in Table I.

Procedure D. 7-Chloro-3-fluoro-5-(2-fluorophenyl)-2,3-dihydro-N-methyl-2-oxo-1H-1,4-benzodiazepine-1-carboxamide (26)

This procedure illustrates the reaction of 3-fluoro-N-unsubstituted benzodiazepines with alkyl isocyanates. Other examples are listed in Table I.

A solution of 0.8 g (2.6 mmol) of 6 and 0.57 g (10 mmol) of methyl isocyanate in 10 ml of benzene was refluxed for two days, and then evaporated to dryness under reduced pressure. The residue was recrystallized from benzene-heptane to give 0.80 g (85%) of 26 as colorless crystals. Spectral and analytical data are in Table I.

Preparation of 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

This procedure illustrates the two-step preparation of 3-hydroxybenzodiazepinones, precursors to the 3-fluorobenzodiazepinones. Other examples are listed in Table II.

A 9.5 g (0.027 mole) portion of 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-oxide was added portion-wise to 50 ml of trifluoroacetic anhydride, and the reaction mixture was stirred for 90 minutes. The suspended solid that formed was collected on a filter, washed thoroughly with pentane, and dried in a vacuum over KOH. There was obtained 9.72 g (80%) of 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-3-trifluoroacetoxy-2H-1,4-benzodiazepin-2-one (nc) as an off-white crystalline powder: mp 175°-177° (dec.); ^{19}F NMR (DMSO-d_6) δ-74.6 ppm (s,3F) and -112.7 ppm (m,1F); ^{1}H NMR (DMSO-d_6) δ 6.34 ppm (s,1H), 7.1-8.1 ppm (m,7H), 11.5 ppm (NH). Anal. Calcd for $C_{17}H_9BrF_4N_2O_3$: C, 45.86; H, 2.04; F, 17.70, N, 6.29. Found: C, 44.55; H, 1.91; F, 18.00; N, 6.31.

A suspension of 9.5 g (0.021 mole) of 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-3-trifluoroacetoxy-2H-1,4-benzodiazepin-2-one in a mixture of 130 ml ethanol and 130 ml aqueous 5% sodium bicarbonate was stirred at 25° for 18 hr. the suspended solid was collected on a filter, washed with water, dried in air, and recrystallized from ethanol to give 4.54 g (62%) 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one as colorless crystals: mp 196°-198°; ^{19}F NMR (DMSO-d_6) δ-113.5 ppm (m); ^{1}H NMR (DMSO-d_6) δ 4.88 ppm (s, 1H), 6.35 ppm (s,OH), 7.0-7.9 ppm (m,7H). Anal. Calcd for $C_{15}H_{10}BrFN_2O_2$: C, 51.59; H, 2.89; F, 5.44; N, 8.02. Found: C, 51.63; H, 2.97; F, 5.41; N, 7.89.

7-Chloro-2-methylamino-5-phenyl-3-trifluoroacetoxy-3H-1,4-benzodiazepine (nc)

Trifluoroacetic anhydride (25.2 g, 0.12 mole) was added dropwise to a stirred mixture of 15 g 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide in 100 ml for dimethylformamide. The reaction mixture warmed spontaneously to 40°, and was held there by slight cooling. The reaction mixture was stirred for 2 hr while it cooled to room temperature, and then it was poured into 100 ml of water and neutralized with 5% aqueous sodium bicarbonate. The solid that formed was

collected on a filter, washed with water, and dried to give 18.03 g (91%) of 7-chloro-2-methylamino-5-phenyl-3-trifluoroacetoxy-3H-1,4-benzodiazepine as a crystalline white powder: mp 124°-126°; ^{19}F NMR (DMSO-d_6) δ-74.6 ppm (s). Anal. Calcd for $C_{18}H_{13}ClF_3N_3O_2$: C, 54.62; H, 3.31; F, 14.40; N, 0.62. Found: C, 53.85; H, 3.65; F, 14.52; N, 9.95.

7-Chloro-3-hydroxy-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (14)

A mixture of 18.7 g (0.047 mole) of 7-chloro-2-methylamino-5-phenyl-3-trifluoroacetoxy-3H-1,4-benzodiazepine, 200 ml of ethanol, and 200 ml of 5% aqueous sodium bicarbonate was stirred overnight. Cold water, 200 ml, was added and the suspended solid was collected on a filter, washed with water, and recrystallized from benzene-heptane to give 12.69 g (90%) of 7-chloro-3-hydroxy-2-methylamino-5-phenyl-3H-1,4-benzodiazepine as colorless crystals, mp 186°-189° [9].

7-Chloro-3-fluoro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one-3d (nc)

A 10 ml portion of deuterium oxide (99.8%) was added to a stirred solution of 30.77 g (0.1 mole) of 4 in 200 ml of very dry dimethylformamide, then 1 ml of 2N NaOD (0.002 mole) in D_2O was added. While stirring was continued, 90 ml of deuterium oxide was slowly added. The resulting mixture was cooled, and the solid that formed was collected on a filter and dried in air. The solid was redissolved in 200 ml of dry dimethylformamide, and the process was repeated. The resulting solid was thoroughly washed with 1% aqueous hydrochloric acid and then recrystallized from ethanol to give 26 g of 7-chloro-3-fluoro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one-3d as colorless crystals: mp 145°-147°; ^{19}F NMR ($CDCl_3$) δ-162.4 ppm (t, J = 8 Hz, 99.1%) and δ-161.6 ppm (d, J = 56 Hz, 0.9%).

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