Synthesis and Spectral Properties of 2-[(*o*- and *p*-Substituted)aminophenyl]-3*H*-5-[(*o*- and *p*-substituted)phenyl]-7-chloro-1,4-benzodiazepines

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To Professor Raymond N. Castle, a great friend

A series of twelve new 2-[(*o*- and *p*-substituted)aminophenyl]-3*H*-5-[(*o*- and *p*-substituted)phenyl]-7-chloro-1,4-benzodiazepines, which have possible pharmacological properties has been obtained. The synthesis was carried out following six steps. The structure of all products was corroborated by ir, ^{1}H nmr, ^{13}C nmr and ms. In addition for the compound 2-(*o*-chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine **7**, its structure was confirmed by X-ray diffraction.

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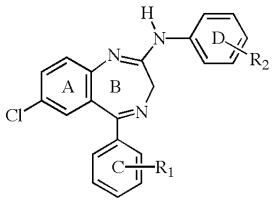
The benzodiazepines have been widely employed in clinical practice as anxiolytics, sedatives-hypnotics, anticonvulsants vasopressin antagonists and HIV reverse transcriptase inhibitors [3-5]. There have been several reports concerning pharmacological activity of benzodiazepines with chloro-substituents in the C-7 position of the benzene ring of the benzodiazepine derivates [6-8]. In the course of the synthesis and property studies of compounds with possible pharmacological activity we have previously reported the synthesis of 2,3-dihydro-2-[(*o*- and *p*-substituted)anilinylene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines [9], 7-[(*o*-, *m*- and *p*-substituted)phenoxy]-1*H*-1,5-benzodiazepine-2-thiones [10,11] and 2-methylthio-7-[(*o*-, *p*-substituted)-phenylthio]-1,5-benzodiazepines [12].

As a part of a program directed toward the synthesis and spectral property determination of 1,4-benzodiazepine derivatives with possible pharmacological activity, we described in this report the synthesis of the novel compounds of 2-[(*o*- and *p*-substituted)aminophenyl]-3*H*-5-[(*o*- and *p*-substituted)phenyl]-7-chloro-1,4-benzodiazepines **VI**, **1-12** (Scheme 1). The synthesis of these compounds was carried out in six steps as shown in Scheme 2.

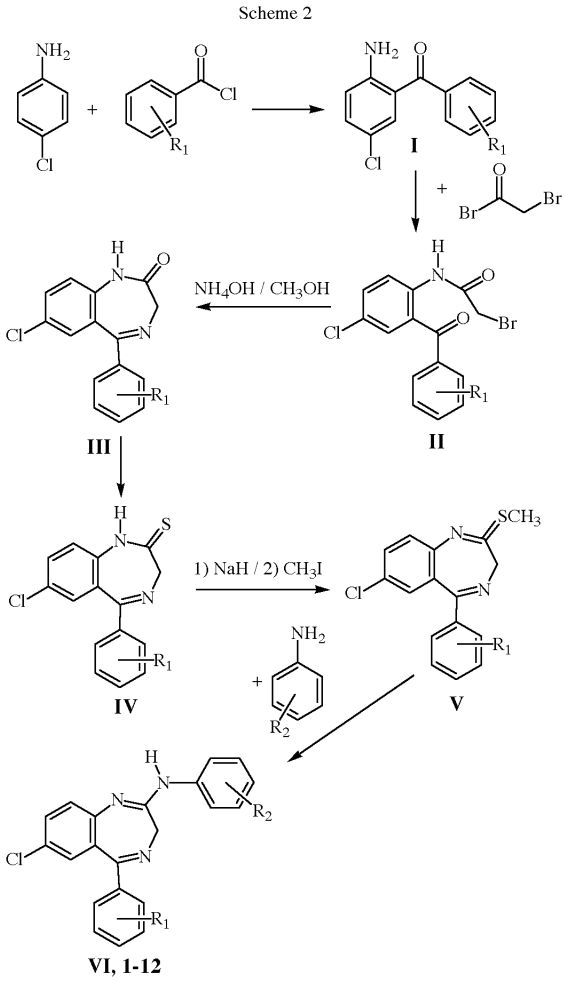
Scheme 1



VI, 1-12

	R_1	R_2
1	o-Cl	o-Cl
2	o-Cl	p-Cl
3	o-Cl	o-OCH_3
4	o-Cl	p-OCH_3
5	p-Cl	o-Cl
6	p-Cl	p-Cl
7	o-F	o-Cl
8	o-F	p-Cl
9	o-F	o-OCH_3
10	o-F	p-OCH_3
11	p-F	o-Cl
12	p-F	p-Cl

Scheme 2



The reaction of *o*- and *p*-substituted-benzoyl chloride with *p*-chloroaniline and zinc chloride was heated at 220-230° for three hours. After the reaction mixture was cooled to 120° and washed with water. The residual semisolid was dissolved with a mixture of H_2SO_4, CH_3COOH, H_2O (2:1:1), the solution was heated at reflux for 17-24 hours, and afforded the [2-amino-5-chlorophenyl]-[(*o*- and *p*-substituted)phenyl] ketones **I**, in 40-44% yield. Treatment of compounds **I** with bromoacetyl bromide in dry ether, with stirring at a constant temperature of 10º for two hours afforded the [2-bromo-acetamide-5-chlorophenyl]-[(*o*- and *p*-substituted)phenyl] ketones **II**, in 94-98% yield.

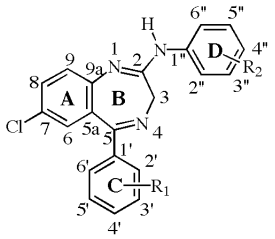
Compound **II** was dissolved in dry ether, subsequently a mixture of ammonium hydroxide/methanol 15% was added and the reaction mixture was stirred at room temperature for 46 hours. The 7-chloro-5-[(*o*- and *p*-substituted)phenyl]-3*H*-1,4-benzodiazepin-2-ones **III** were obtained in 60-80% yield.

A mixture of compounds **III** and Lawesson's reagent in dry toluene was heated at reflux under a nitrogen atmosphere for 1.5 hours, the thione, which was not isolated, was treated with sodium hydride and methyl iodide at reflux for one hour to afford compounds **V** in 60-70% yield.

A mixture of 2-methylthio-5-[(*o*- and *p*-substituted)phenyl]-7-chloro-3*H*-1,4-benzodiazepine **V** and the corresponding (*o*-and *p*-substituted)aniline in the presence of a few drops of acetic acid at reflux in anhydrous toluene for one hour, afforded the 2-[(*o*- and *p*-substituted)aminophenyl]-3*H*-5-[(*o*-and *p*-substituted)phenyl]-7-chloro-1,4-benzodiazepines **VI**, **1-12** in 50-84% yield.

The infrared spectrum of compounds **1-12** displayed absorptions at 3441-3286 cm^{-1} for N-H stretching, at 1636-1612 cm^{-1} for C=N stretching, at 1360-1344 and 1312-1292 cm^{-1} for C-N stretching as well as the corresponding absorptions for aromatic and R-substituents.

Table 1
^{13}C NMR Spectral Data for Compounds **VI**, **1-12**



VI, 1-12

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
R_1	*o*-Cl	*o*-Cl	*o*-Cl	*o*-Cl	*p*-Cl	*p*-Cl	*o*-F	*o*-F	*o*-F	*o*-F	*p*-F	*p*-F
R_2	*o*-Cl	*p*-Cl	*o*-OCH_3	*p*-OCH_3	*o*-Cl	*p*-Cl	*o*-Cl	*p*-Cl	*o*-OCH_3	*p*-OCH_3	*o*-Cl	*p*-Cl
C2	150.9	151.4	150.7	152.0	152.2	152.2	151.4	151.8	151.2	152.2	152.5	152.5
C3	55.1	53.4	55.5	54.0	55.2	54.6	55.1	53.5	55.4	54.3	54.9	54.4
C5	169.7	168.2	169.4	170.1	169.3	169.8	167.0	165.9	166.8	167.3	169.3	170.0
C5a	126.7	124.8	126.1	125.8	126.6	126.3	127.0	125.3	126.3	125.9	126.6	126.3
C6	128.7	127.8	128.7	128.7	129.9	129.9	129.0	128.2	129.0	129.0	130.0	130.0
C7	129.2	128.6	128.9	128.9	128.2	127.9	129.3	128.7	129.2	129.1	128.1	128.1
C8	130.6	130.1	130.5	130.6	131.3	131.4	131.2	130.3	131.0	131.1	131.3	131.4
C9	128.3	128.0	128.6	128.4	128.3	128.3	128.2	127.1	128.5	128.4	128.3	128.3
C9a	147.4	147.7	147.7	148.4	148.5	148.8	147.0	147.1	147.9	148.3	148.2	148.9
C1'	138.5	138.2	138.7	138.7	137.5	137.4	127.3 (d) $^2J_{C-F}$=12.1	127.0 (d) $^2J_{C-F}$=13.2	127.5 (d) $^2J_{C-F}$=12.1	127.5 (d) $^2J_{C-}$=13.2	135.2 (d) $^4J_{C-F}$=3.3	135.2 (d) $^4J_{C-F}$=3.2
C2'	133.4	132.3	133.4	133.4	131.2	131.2	160.5 (d) $^1J_{C-F}$=252.5	159.8 (d) $^1J_{C-F}$=251.0	160.5 (d) $^1J_{C-F}$=252.5	160.5 (d) $^1J_{C-F}$=252.5	131.9 (d) $^3J_{C-F}$=8.7	131.9 (d) $^3J_{C-F}$=7.7
C3'	130.1	129.3	130.1	130.1	128.6	128.7	116.4 (d) $^2J_{C-F}$=22.0	115.5 (d) $^2J_{C-F}$=21.9	116.2 (d) $^2J_{C-F}$=20.9	116.3 (d) $^2J_{C-F}$=21.9	115.4 (d) $^2J_{C-F}$=22.0	115.5 (d) $^2J_{C-F}$=20.8
C4'	131.1	130.0	131.0	131.1	136.6	136.8	131.9 (d) $^3J_{C-F}$=8.8	131.1 (d) $^3J_{C-F}$=7.7	131.8 (d) $^3J_{C-F}$=7.7	131.9 (d) $^3J_{C-F}$=8.8	164.2 (d) $^1J_{C-F}$=250.0	164.3 (d) $^1J_{C-F}$=250.0
C5'	126.8	126.4	126.7	126.7	128.6	128.6	124.2 (d) $^4J_{C-F}$=4.4	123.6 (d) $^4J_{C-F}$=4.4	124.1 (d) $^4J_{C-F}$=3.2	124.1 (d) $^4J_{C-F}$=4.4	115.4 (d) $^2J_{C-F}$=22.0	115.5 (d) $^2J_{C-F}$=20.8
C6'	131.1	130.8	131.1	131.1	131.2	131.2	131.6 (d) $^3J_{C-F}$=8.7	131.1 (d) $^3J_{C-F}$=7.7	131.8 (d) $^3J_{C-F}$=7.7	131.9 (d) $^3J_{C-F}$=8.7	131.9 (d) $^3J_{C-F}$=8.7	131.9 (d) $^3J_{C-F}$=7.7
C1"	136.0	138.6	129.0	132.1	135.8	137.5	135.7	138.1	128.7	132.1	135.7	137.6
C2"	122.6	120.2	148.3	131.1	122.6	121.2	122.8	120.4	147.9	131.7	122.7	121.2
C3"	129.0	127.9	109.7	114.0	129.0	128.8	129.0	127.9	109.8	114.0	129.0	128.7
C4"	124.0	126.5	123.1	156.3	124.0	128.9	124.1	128.7	123.2	156.3	124.1	128.8
C5"	127.6	127.9	120.9	114.0	127.5	128.8	127.6	127.9	120.9	114.0	127.5	128.7
C6"	121.0	120.2	119.3	131.1	121.0	121.2	121.1	120.4	119.5	131.7	121.1	121.2
R_2	--	--	55.6	55.4	--	--	--	--	55.7	54.4	--	--

NOTE: The numbering of phenyl rings is only for the assignment of the chemical shifts of the carbon atoms of the ^{13}C nmr spectra.

In the ^{1}H-nmr spectra the presence of two broad proton signals at δ 3.60-4.80 is consistent with the methylene protons at C-3. The presence of a three protons multiplet signal at δ 6.93-7.44 was assigned to the aromatic protons at C-6, C-8 and C-9 of the benzodiazepine framework. The other aromatic resonances appeared as a multiplet and an AA'BB' system at δ 6.77-8.71 and with the signal for the R-substituents.

The ^{13}C-nmr spectra of compounds **1-12** are given in Table 1. The signals were confirmed by using HETCOR, long range HETCOR, COSY and NOESY nmr experiments operating at 500 MHz.

The mass spectra of compounds **1-12** include the molecular ion $[M]^+$ as the base peak when the R_2-substituent is attached in the *para*-position whereas $[M-R_2]^+$ is the base peak when the R_2-substituent is attached in the *ortho*-position. Other important fragments are: $[M-1]^+$, $[M-R_1]^+$, $[M-63]^+$, $[M-(63+HR_2)]^+$, $[M-(76+R_2)]^+$, $[240+R_1]^+$, $[213+R_1]^+$, $[204+R_1]^+$, m/z 163 and $[90+R_2]^+$.

The mass spectra of the compounds exhibit a stable molecular ion and the main fragmentation is consistent with the assigned structures. The proposed fragmentation pathways leading to the formation of a number of important daughter ions have been confirmed by the corresponding parent ion spectra using collision-induced dissociation experiments. The elemental composition of the molecular ion and the principal fragment ion was determined by exact mass measurements.

In order to confirm the structure of the compounds **VI**, **1-12**, an X-ray crystal structure determination was carried out for the 2-(*o*-chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine **7**. Figure 1 shows the molecular structure together with the atom numbering scheme. Selected bond distances (Å) and the angles (deg) are given in Table 2. The results confirm that the length of C_2-N_3 bond length value of 1.363(4) Å is significantly shorter than that of the normal C-N bond (1.48 Å). This is presumably due to some delocalization of the ring-nitrogen atom's lone pair. In contrast the C_2-N_1 bond is very similar to that of the normal C=N double bond, [13-14] where, in this case, the 1,4-benzodiazepines double bond is endocyclic. Crystal data collection parameters and structure refinement parameters for the compound **7**, are given in Table 3.

Table 2
Bond Distances (Å) and the Angles (deg) for the 2-(*o*-Chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**7**) with Standard Deviations in Parentheses

Cl(1)-C(7)	1.751 (3)	Cl (2)-C(19)	1.743 (4)
N(3)-C(2)	1.363 (4)	N(3)-C(18)	1.412 (4)
N(1)-C(2)	1.284 (4)	N(1)-C(10)	1.399 (4)
C(2)-C(3)	1.516 (4)	C(3)-N(4)	1.470 (4)
N(4)-C(5)	1.291 (4)	C(5)-C(11)	1.484 (4)
C(5)-C(12)	1.498 (5)	C(6)-C(7)	1.375 (5)
C(6)-C(11)	1.404 (4)	C(7)-C(8)	1.380 (5)
C(8)-C(9)	1.370 (5)	C(9)-C(10)	1.410 (4)
C(10)-C(11)	1.404 (4)	C(12)-C(13)	1.386 (5)
C(12)-C(17)	1.395 (5)	C(13)-F(1)	1.272 (5)
C(13)-C(14)	1.375 (6)	C(14)-C(15)	1.378 (6)
C(15)-C(16)	1.362 (6)	C(16)-C(17)	1.381 (6)
C(18)-C(23)	1.389 (5)	C(18)-C(19)	1.394 (5)
C(19)-C(20)	1.376 (5)	C(20)-C(21)	1.370 (5)
C(21)-C(22)	1.387 (5)	C(22)-C(23)	1.373 (5)
C(17)-F(2)	1.196 (6)		
C(2)-N(3)-C(18)	127.6 (3)	C(2)-N(1)-C(10)	119.7 (3)
N(1)-C(2)-N(3)	123.0 (3)	N(1)-C(2)-C(3)	121.0 (3)
N(3)-C(2)-C(3)	115.9 (3)	N(4)-C(3)-C(2)	106.3 (3)
C(5)-N(4)-C(3)	115.7 (3)	N(4)-C(5)-C(11)	125.1(3)
N(4)-C(5)-C(12)	116.6 (3)	C(11)-C(5)-C(12)	118.2 (3)
C(7)-C(6)-C(11)	120.1 (3)	C(6)-C(7)-C(8)	121.3 (3)
C(6)-C(7)-Cl(1)	118.7 (3)	C(8)-C(7)-Cl(1)	119.9 (3)
C(9)-C(8)-C(7)	118.8 (3)	C(8)-C(9)-C(10)	122.3 (4)
N(1)-C(10)-C(11)	125.1 (3)	N(1)-C(10)-C(9)	116.7(3)
C(11)-C(10)-C(9)	117.7 (3)	C(10)-C(11)-C(6)	119.7 (3)
C(10)-C(11)-C(5)	122.5 (3)	C(6)-C(11)-C(5)	117.8 (3)
C(13)-C(12)-C(17)	116.8 (3)	C(13)-C(12)-C(5)	121.2 (3)
C(17)-C(12)-C(5)	122.0 (3)	F(1)-C(13)-C(14)	116.7 (4)
F(1)-C(13)-C(12)	121.3 (4)	C(14)-C(13)-C(12)	122.0 (4)
C(13)-C(14)-C(15)	119.4 (4)	C(16)-C(15)-C(14)	120.0 (4)
C(15)-C(16)-C(17)	119.9 (4)	C(23)-C(18)-C(19)	117.4 (3)
C(23)-C(18)-N(3)	122.6 (3)	C(19)-C(18)-N(3)	119.9 (3)
C(20)-C(19)-C(18)	121.5 (3)	C(20)-C(19)-Cl(2)	118.6 (3)
C(18)-C(19)-Cl(2)	119.9 (3)	C(21)-C(20)-C(19)	120.5 (4)
C(20)-C(21)-C(22)	118.8 (4)	C(23)-C(22)-C(21)	120.9 (4)
C(22)-C(23)-C(18)	120.9 (3)	F(2)-C(17)-C(16)	115.5 (5)
F(2)-C(17)-C(12)	123.0 (4)	C(16)-C(17)-C(12)	121.4 (4)

Symmetry transformations used to generate equivalent atoms:

Table 3
Crystal Data Collection Parameters and Structure Refinement Parameters of the 2-(*o*-Chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**7**).

Crystals dimensions (mm^3)	0.40 x 0.20 x 0.08	Temperature (K)	293 (2)
M	397.24	Crystal system/Space group	Monoclinic/C_2/c
Unit cell dimensions		V ($Å^3$)	3744.6 (8)
a (Å)	17.020 (2)	Z	8
b (Å)	8.135 (1)	Dc ($g.cm^3$)	1.409
c (Å)	27.579 (3)	F(000)	1624
β (°)	101.29 (1)	Data collection method	XSCANS
Absorption coefficient (mm^{-1})	0.367	Reflections measured	3423
θ Range (°)	2.44 to 25.00	Scan type	ω-2θ
Independent reflections /Rint	3305/0.0306	R_1(obs)/R_1(all refl.)	0.0459/0.1013
wR_2(obs)/wR_2(all refl.)	0.0931/0.1087	Goof (F^2)	0.818
Extinction coefficient	0.0009 (2)	System solution	SHELXS 97
Weighting scheme	$1/[\sigma^2(Fo^2)+(0.0406)^2+0.00P]$ with $P=(Fo^2+2Fc^2)/3$		

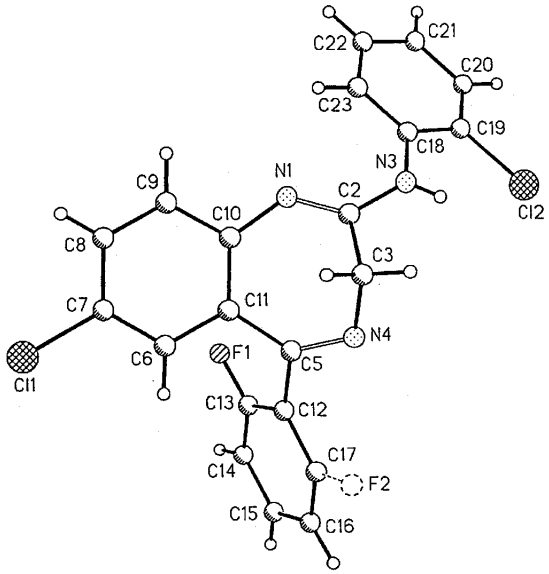


Figure 1. Crystal structure of compound **7** with the atom numbering scheme

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian Unity 300 spectrometer operating at 300 MHz and the ^{13}C-nmr spectra were recorded on a Varian Unity 500 MHz spectrometer operating at 500 MHz in deuteriochloroform solution or deuteriodimethyl sulfoxide solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfield from tetramethylsilane. The mass spectra were measured on a Joel JMS-AX505 and Jeol MS-SX 102A high resolution mass spectrometer with accurate mass determination of the molecular ion and the principal fragments ions, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190° and ionizing electron energy of 70 eV.

General Procedure for the Synthesis of the [2-Amino-5-chlorophenyl] [(*o*- and *p*-substituted)-phenyl] Ketones **I**.

A stirred solution of 0.021 mole of either (*o*- or *p*-substituted)-benzoyl chloride was heated to 120º, then 0.0042 mole of *p*-chloroaniline was added slowly. Once the *p*-chloroaniline dissolved, 0.0042 mole of zinc chloride was added increasing the temperature up to 200-230°. The reaction mixture was heated at reflux for three hours, after which the reaction mixture was cooled to 120° and washed with water. The residual semisolid was dissolved with a mixture of sulfuric acid, acetic acid and water (2:1:1), then the solution was heated at reflux for 17-24 hours, after which the reaction mixture was poured into ice-water, extracted with dichloromethane and washed with 15% aqueous ammonium hydroxide solution and water at pH 7. The organic phase was dried over sodium sulphate, filtered and evaporated *in vacuo* to yield a solid. The residual solid was purified on a silica gel chromatography column that was eluted with hexane-ethyl acetate (98:2) to yield a yellow solid, compounds **I** (40-44%).

General Procedure for the Synthesis of the [2-Bromoacetamide-5-chlorophenyl]-[(*o*- and *p*-substituted)phenyl] Ketones **II**.

A stirred solution of either [2-amino-5-chlorophenyl]-[(*o*- or *p*-substituted)-phenyl] ketone **I** (0.015 mole) in dry ether was cooled in ice-water to 10°. Subsequently 0.037 mole of bromoacetyl bromide was added and stirred and a temperature of 10° was maintained for two hours. The reaction mixture was then washed with 5% aqueous ammonium hydroxide solution, and the remaining ether layer was dried over sodium sulphate, filtered and evaporated *in vacuo* to yield colorless solid, compounds **II**, in 94-98% yield.

General Procedure for the Synthesis of the 7-Chloro-5-[(*o*- and *p*-substituted)phenyl]-3*H*-1,4-benzodiazepin-2-ones **III**.

In a two neck round bottom flask equipped with a dry-ice condenser and an exhaust valve, 0.016 mole of [2-bromoacetamide-5-chlorophenyl]-[(*o*- and *p*-substituted)phenyl] ketone **II** was dissolved in 100 ml of dry ether. Subsequently a mixture of ammonium hydroxide/methanol 15% (180 ml) was added and the reaction mixture was stirred at room temperature for 46 hours. The reaction was monitored by thin layer chromatography until the reaction was finished, at which time a mixture of ether/water was added. The organic phase was dried over sodium sulphate, filtered and evaporated *in vacuo* to yield a residual solid. The residual solid was purified on a silica gel chromatography column and that was eluted with hexane-ethyl acetate (98:2) to yield a white solid, compounds **III** in 60-80% yield.

General Procedure for the Synthesis of the 7-Chloro-5-[(*o*- and *p*-substituted)phenyl]-3*H*-1,4-benzodiazepin-2-thiones **IV**.

A mixture of 0.009 mole of either 7-chloro-5-[(*o*- or *p*-substituted)phenyl]-3*H*-1,4-benzodiazepin-2-one **III** and 0.0045 mole of Lawesson´s reagent in dry toluene was heated at reflux under a nitrogen atmosphere for 1.5 hours. The reaction product was not isolated.

General Procedure for the Synthesis of the 2-Methylthio-5-[(*o*- and *p*- substituted)phenyl]-7-chloro-3*H*-1,4-benzodiazepine **V**.

In a two neck round bottom flask, 0.027 mole of sodium hydride in toluene was added to the solution of thione from the previous step and heated at reflux for one hour. After the reaction mixture was cooled to room temperature, 0.027 mole of methyl iodide was added dropwise over a few minutes and the reflux continued for one hour. The reaction mixture was cooled to room temperature, filtered and the organic solution was dried over sodium sulphate, filtered and evaporated *in vacuo* to yield an oil. The residual oil was purified on a silica gel chromatography column and elution with hexane-ethyl acetate (95:5) to yield an orange semisolid. The total yield of the previous stage and this reaction was of 60-70% for the compounds **V**.

General Procedure for the Synthesis of the 2-[(*o*- and *p*-Substituted)aminophenyl]-3*H*-5-[(*o*- and *p*-substituted)phenyl]-7-chloro-1,4-benzodiazepines **VI**, **1-12**.

A stirred solution of either 2-methylthio-5-[(*o*- or *p*-substituted)phenyl]-7-chloro-3*H*-1,4-benzodiazepine **V** (0.0006 mole) in anhydrous toluene and five drops of acetic acid was kept under nitrogen atmosphere at reflux for one hour. Subsequently, a solution of the corresponding *o*- or *p*-substituted-aniline (0.0013 mole) in the same solvent (5.0 ml), was added dropwise over a period of a few minutes, and the reflux was continued for

24-48 hours. The reaction mixture was cooled and washed with water (3 x 15 ml). The organic phase was dried over sodium sulphate, filtered and evaporated *in vacuo* to yield a solid. The residual solid was purified by crystallization from dichloromethane-hexane to yield the compounds **VI**, **1-12** in 50-84% yield.

2-(*o*-Chloroaminophenyl)-3*H*-5-(*o*-chlorophenyl)-7-chloro-1,4-benzodiazepine (**1**).

This compound was obtained as white needles in 76% yield, mp 204°; ir (chloroform): υ N-H 3419, C=N 1636, C-N 1346 and 1308 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.24 (bs, 2H, 3-H), 7.00 (dt, 1H, J = 1.5, 7.5 Hz, 4"-H), 7.04 (d, 1H, J = 2.4 Hz, 6-H), 7.26 (d, 1H, J = 8.7 Hz, 9-H), 7.27 (dt, 1H, J = 1.5, 8.1 Hz, 5"-H), 7.34 (dt, 1H, J = 2.0, 7.5 Hz, 5'-H), 7.35 (dd, 1H, J = 1.2, 7.8 Hz, 3"-H), 7.36 (dd, 1H, J = 2.0, 7.5 Hz, 3'-H), 7.37 (dt, 1H, J = 2.0, 7.5 Hz, 4'-H), 7.38 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.46 (dd, 1H, J = 3.0, 7.5 Hz, 6'-H), 8.67 (dd, 1H, J = 1.2, 8.1 Hz, 6"-H), 870 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 413 $(M)^+$, 415 $[M+2]^+$; 417 $[M+4]^+$; 419$[M+6]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_3N_3$: C, 60.82; H, 3.40; N, 10.14. Found: C, 60.91; H, 3.33; N, 10.21.

2-(*p*-Chloroaminophenyl)-3*H*-5-(*o*-chlorophenyl)-7-chloro-1,4-benzodiazepine (**2**).

This compound was obtained as yellowish needles in 80% yield, mp 240°; ir (chloroform): υ N-H 3286, C=N 1630, C-N 1360 and 1312 cm^{-1}; ^1H nmr (deuteriochloroform and deuteriodimethyl sulfoxide): δ 4.26 (bs, 2H, 3-H), 6.93 (d, 1H, J = 2.7 Hz, 6-H), 7.19 (d, 1H, J = 8.7 Hz, 9-H), 7.23 and 7.83 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.35 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.37 (dt, 1H, J = 2.0, 7.5 Hz, 5'-H), 7.38 (dd, 1H, J = 2.0, 7.5 Hz, 3'-H), 7.39 (dt, 1H, J = 2.0, 7.5 Hz, 4'-H), 7.49 (dd, 1H, J = 3.0, 7.5 Hz, 6'-H), 9.69 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 413 $(M)^+$, 415 $[M+2]^+$, 417 $[M+4]^+$; 419 $[M+6]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_3N_3$: C, 60.82; H, 3.40; N, 10.14. Found: C, 60.74; H, 3.48; N, 10.05.

2-(*o*-Methoxyaminophenyl)-3*H*-5-(*o*-chlorophenyl)-7-chloro-1,4-benzodiazepine (**3**).

This compound was obtained as white needles in 70% yield, mp 178°; ir (chloroform): υ N-H 3423, C=N 1636, C-N 1356 and 1292, C-O 1247 and 1030 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.87 (s, 3H, C2"-OCH_3), 4.23 (bs, 2H, 3-H), 6.86 (dd, 1H, J = 2.4, 7.8 Hz, 3"-H), 6.96 (dt, 1H, J = 2.4, 7.8 Hz, 5"-H), 6.99 (dt, 1H, J = 2.4, 7.5 Hz, 4"-H), 7.02 (d, 1H, J = 2.7 Hz, 6-H), 7.29 (d, 1H, J = 8.7 Hz, 9-H), 7.31 (dt, 1H, J = 2.0, 7.5 Hz, 5'-H), 7.34 (dd, 1H, J = 2.0, 7.2 Hz, 3'-H), 7.35 (dt, 1H, J = 2.0, 7.2 Hz, 4'-H), 7.38 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.43 (dd, 1H, J = 3.0, 7.5 Hz, 6'-H), 8.71 (dd, 1H, J = 1.5, 7.8 Hz, 6"-H), 8.71 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 409 $(M)^+$, 411 $[M+2]^+$; 413 $[M+4]^+$.

Anal. Calcd. for: $C_{22}H_{17}Cl_2N_3O$: C, 64.40; H, 4.18; N, 10.24. Found: C, 64.49; H, 4.10; N, 10.33.

2-(*p*-Methoxyaminophenyl)-3*H*-5-(*o*-chlorophenyl)-7-chloro-1,4-benzodiazepine (**4**).

This compound was obtained as greenish needles in 73% yield, mp 172°; ir (chloroform): υ N-H 3441, C=N 1626, C-N 1346 and 1298, C-O 1245 and 1036 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.75 (s, 3H, C4"-OCH_3), 4.19 (bs, 2H, 3-H), 6.77 and 7.32 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.00 (d, 1H, J = 2.1 Hz, 6-H), 7.20 (d, 1H, J = 8.7 Hz, 9-H), 7.31 (dt, 1H, J = 2.0, 7.5 Hz, 5'-H), 7.33 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 7.34 (dd, 1H, J = 2.0, 7.2 Hz, 3'-H), 7.35 (dt, 1H, J = 2.0, 7.2 Hz, 4'-H), 7.43 (dd, 1H, J = 3.0, 7.5 Hz, 6'-H), 8.91 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 409 $(M)^+$, 411 $[M+2]^+$; 413 $[M+4]^+$.

Anal. Calcd. for: $C_{22}H_{17}Cl_2N_3O$: C, 64.40; H, 4.18; N, 10.24. Found: C, 64.32; H, 4.27; N, 10.30.

2-(*o*-Chloroaminophenyl)-3*H*-5-(*p*-chlorophenyl)-7-chloro-1,4-benzodiazepine (**5**).

This compound was obtained as yellowish needles in 57% yield, mp 148°; ir (chloroform): υ N-H 3417, C=N 1634, C-N 1348 and 1306 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65 and 4.74 (bs, 2H, 3-H), 7.00 (dt, 1H, J = 1.5, 7.8 Hz, 4"-H), 7.25 (d, 1H, J = 2.1 Hz, 6-H), 7.25 (dt, 1H, J = 1.5, 7.5 Hz, 5"-H), 7.28 (d, 1H, J = 8.7 Hz, 9-H), 7.35 (dd, 1H, J = 1.5, 7.8 Hz, 3"-H), 7.37 and 7.50 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "C" ring), 7.43 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 8.10 (dd, 1H, J = 1.8, 8.1 Hz, 6"-H), 8.71 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 413 $(M)^+$, 415 $[M+2]^+$; 417 $[M+4]^+$; 419 $[M+6]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_3N_3$: C, 60.82; H, 3.40; N, 10.14. Found: C, 60.89; H, 3.34; N, 10.21.

2-(*p*-Chloroaminophenyl)-3*H*-5-(*p*-chlorophenyl)-7-chloro-1,4-benzodiazepine (**6**).

This compound was obtained as brown needles in 50% yield, mp 197°; ir (chloroform): υ N-H 3439, C=N 1630, C-N 1348 and 1304 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.60 and 4.80 (bs, 2H, 3-H), 7.17 and 7.41 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 7.24 (d, 1H, J = 2.7 Hz, 6-H), 7.27 (d, 1H, J = 8.7 Hz, 9-H), 7.43 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 7.37 and 7.50 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "C" ring), 9.10 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 413 $(M)^+$, 415 $[M+2]^+$; 417 $[M+4]^+$; 419 $[M+6]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_3N_3$: C, 60.82; H, 3.40; N, 10.14. Found: C, 60.92; H, 3.31; N, 10.06.

2-(*o*-Chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**7**).

This compound was obtained as brownish needles in 80% yield, mp 155°; ir (chloroform): υ N-H 3422, C=N 1636, C-N 1356 and 1306 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.24 (bs, 2H, 3-H), 7.01 (dt, 1H, J = 1.5, 7.8 Hz, 4"-H), 7.08 (dd, 1H, J_{H-H} = 1.2, J_{H-H} = 8.4, $J_{H-F}{}^1$ = 9.6 Hz, 3'-H), 7.22 (dt, 1H, J_{H-H} = 1.2, J_{H-H} = 7.5 Hz, 5'-H), 7.25 (d, 1H, J = 3.0 Hz, 6-H), 7.27 (dt, 1H, J = 1.5, 7.8 Hz, 5"-H), 7.29 (d, 1H, J = 9.0 Hz, 9-H), 7.36 (dd, 1H, J = 1.5, 8.1 Hz, 3"-H), 7.42 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.45 (dt, 1H, J_{H-H} = 1.2, J_{H-H} = 8.4, $J_{H-F}{}^2$ = 5.5 Hz, 4'-H), 7.52 (dd, 1H, J_{H-H} = 1.8, J_{H-H} = 7.5, $J_{H-F}{}^2$ = 7.3 Hz, 6'-H), 8.70 (d, 1H, J = 6.0 Hz, 6"-H), 8.70 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 397 $(M)^+$; 399 $[M+2]^+$; 401 $[M+4]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_2FN_3$: C, 63.33; H, 3.54; N, 10.55. Found: C, 63.44; H, 3.59; N, 10.61.

2-(*p*-Chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**8**).

This compound was obtained as brownish needles in 82% yield, mp 220°; ir (chloroform): υ N-H 3286, C=N 1612, C-N 1360 and 1306 cm^{-1}; ^1H nmr (deuteriochloroform and deuteriodimethyl sulfoxide): δ 4.25 (bs, 2H, 3-H), 7.07 (dd, 1H,

J_{H-H} = 0.9, J_{H-H} = 8.4, J_{H-F}^1 = 9.3 Hz, 3'-H), 7.12 (d, 1H, J = 2.1 Hz, 6-H), 7.21 (dt, 1H, J_{H-H} = 1.2, J_{H-H} = 7.5 Hz, 5'-H), 7.24 and 7.76 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.25 (d, 1H, J = 8.7 Hz, 9-H), 7.37 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 7.45 (dt, 1H, J_{H-H} = 1.8, J_{H-H} = 8.1, J_{H-F}^2 = 5.1 Hz, 4'-H), 7.52 (dd, 1H, J_{H-H} = 1.8, J_{H-H} = 7.5, J_{H-F}^2 = 7.2 Hz, 6'-H), 9.20 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 397 $(M)^+$, 399 $[M+2]^+$; 401 $[M+4]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_2FN_3$: C, 63.33; H, 3.54; N, 10.55. Found: C, 63.40; H, 3.62; N, 10.48.

2-(*o*-Methoxyaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**9**).

This compound was obtained as brownish needles in 73% yield, mp 183°; ir (chloroform): υ N-H 3423, C=N 1636, C-N 1356 and 1310, C-O 1246 and 1037 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.86 (s, 3H, C2"-OCH_3), 4.38 (bs, 2H, 3-H), 6.86 (dd, 1H, J = 1.8, 7.8 Hz, 3"-H), 6.97 (dt, 1H, J = 1.8, 7.5 Hz, 5"-H), 7.00 (dt, 1H, J = 1.8, 7.5 Hz, 4"-H), 7.08 (dd, 1H, J_{H-H} = 0.9, J_{H-H} = 8.5, J_{H-F}^1 = 9.5 Hz, 3'-H), 7.16 (d, 1H, J = 2.1 Hz, 6-H), 7.19 (dt, 1H, J_{H-H} = 1.2, J_{H-H} = 7.5 Hz, 5'-H), 7.31 (d, 1H, J = 8.7 Hz, 9-H), 7.40 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.43 (dt, 1H, J_{H-H} = 1.8, J_{H-H} = 8.1, J_{H-F}^2 = 5.4 Hz, 4'-H), 7.49 (dd, 1H, J_{H-H} = 1.8, J_{H-H} = 7.5, J_{H-F}^2 = 7.3 Hz, 6'-H), 8.69 (d, 1H, J = 6.6 Hz, 6"-H), 8.96 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 393 $(M)^+$, 395 $[M+2]^+$.

Anal. Calcd. for: $C_{22}H_{17}ClFN_3O$: C, 67.09; H, 4.35; N, 10.67. Found: C, 67.00; H, 4.42; N, 10.76.

2-(*p*-Methoxyaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**10**).

This compound was obtained as greenish needles in 84% yield, mp 179°; ir (chloroform): υ N-H 3441, C=N 1626, C-N 1348 and 1302, C-O 1248 and 1036 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.75 (s, 3H, C4"-OCH_3), 4.42 (bs, 2H, 3-H), 6.77 and 7.36 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "D" ring), 7.06 (dd, 1H, J_{H-H} = 1.2, J_{H-H} = 8.4, J_{H-F}^1 = 9.9 Hz, 3'-H), 7.14 (d, 1H, J = 3.0 Hz, 6-H), 7.17 (dt, 1H, J_{H-H} = 1.2, J_{H-H} = 7.6 Hz, 5'-H), 7.23 (d, 1H, J = 8.7 Hz, 9-H), 7.36 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 7.41 (dt, 1H, J_{H-H} = 1.8, J_{H-H} = 8.1, J_{H-F}^2 = 5.6 Hz, 4'-H), 7.46 (dd, 1H, J_{H-H} = 1.8, J_{H-H} = 7.5, J_{H-F}^2 = 7.2 Hz, 6'-H), 9.10 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 393 $(M)^+$; 395 $[M+2]^+$.

Anal. Calcd. for: $C_{22}H_{17}ClFN_3O$: C, 67.09; H, 4.35; N, 10.67. Found: C, 67.21; H, 4.30; N, 10.60.

2-(*o*-Chloroaminophenyl)-3*H*-5-(*p*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**11**).

This compound was obtained as orange needles in 64% yield, mp 153°; ir (chloroform): υ N-H 3417, C=N 1634, C-N 1344 and 1306 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.66 and 4.72 (bs, 2H, 3-H), 7.01 (dt, 1H, J = 1.8, 7.8 Hz, 4"-H), 7.09 (AA'BB', 2H, J_{H-H} = 8.8, J_{H-F}^1 = 9.3 Hz, phenyl protons , H-3' and H-5' of "C" ring), 7.26 (dt, 1H, J = 1.8, 7.8 Hz, 5"-H), 7.27 (d, 1H, J = 2.4 Hz, 6-H), 7.29 (d, 1H, J = 9.0 Hz, 9-H), 7.36 (dd, 1H, J = 1.8, 7.8 Hz, 3"-H), 7.44 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 7.56 (AA'BB', 2H, J_{H-H} = 8.8 and J_{H-F}^2 = 5.4 Hz, phenyl protons H-2' and H-6' of "C" ring), 8.69 (dd, 1H, J = 1.8, 6.6 Hz, 6"-H), 8.96 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 397 $(M)^+$, 399 $[M+2]^+$; 401 $[M+4]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_2FN_3$: C, 63.33; H, 3.54; N, 10.55. Found: C, 63.22; H, 3.62; N, 10.63.

2-(*p*-Chloroaminophenyl)-3*H*-5-(*p*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**12**).

This compound was obtained as red needles in 66% yield, mp 130°; ir (chloroform): υ N-H 3439, C=N 1630, C-N 1348 and 1304 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 and 4.86 (bs, 2H, 3-H), 7.08 (AA'BB', 2H, J_{H-H} = 9.0, J_{H-F}^1 = 9.6 Hz, phenyl protons , H-3' and H-5' of "C" ring), 7.10 and 7.29 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.27 (d, 1H, J = 2.7 Hz, 6-H), 7.27 (d, 1H, J = 8.7 Hz, 9-H), 7.43 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.57 (AA'BB', 2H, J_{H-H} = 9.0 and J_{H-F}^2 = 5.4 Hz, phenyl protons H-2' and H-6' of "C" ring), 9.15 (bs, 1H, N-H deuterium oxide exchangeable); ms: m/z 397 $(M)^+$, 399 $[M+2]^+$; 401 $[M+4]^+$.

Anal. Calcd. for: $C_{21}H_{14}Cl_2FN_3$: C, 63.33; H, 3.54; N, 10.55. Found: C, 63.26; H, 3.60; N, 10.44.

X-Ray Structure Determinations for Compound (**7**).

Appropriate crystals of 2-(*o*-chloroaminophenyl)-3*H*-5-(*o*-fluorophenyl)-7-chloro-1,4-benzodiazepine (**7**) were obtained by cooling of chloroform.

The X-ray experiments were carried out on a single crystal diffractometer Siemens P4/PC with graphite monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods followed by different Fourier techniques and refined by a full-matrix least squares procedure on F^2 [15]. Anisotropic displacement parameters have been applied for all non-hydrogen atoms.

More details on data collections and structure determinations are summarized in Table 3.

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