Synthesis and Spectral Properties of 2,3-Dihydro-2-[(*o*- and *p*-substituted)anilinylidene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines

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A series of twelve new 2,3-dihydro-2-[(*o*- and *p*-substituted)anilinylidene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines, which have potentially useful pharmacological properties, has been synthesized by condensing the 3,3-dimercapto-1-(*p*-methylphenyl)-2-propen-1-one with 3,4-diaminophenyl-R-phenyl ethers. Subsequently the 1*H*-1,5-benzodiazepine-2-thiones obtained were treated with the (*o*- and *p*-substituted)aniline. The structure of all products was corroborated by ir, ^{1}H nmr, ^{13}C nmr and ms.

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In the course of synthesis and spectral property studies of compounds with possible pharmacological activity, we have previously reported the synthesis of 7-[(*o*-, *m*- and *p*-substituted)phenoxy]-1*H*-1,5-benzodiazepine-2-thiones [3,4], 2-methylthio 7-[(*o*- and *p*-substituted)phenylthio]-1,5-benzodiazepines [5], and 5-methylthio-9-[(*m*- and *p*-substituted)phenoxy][1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepines [6]. 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 derivatives [7-9]. On the other hand, research has been carried out recently and anticonvulsant effects were evaluated in 1,5-benzodiazepin-2-one derivatives [10].

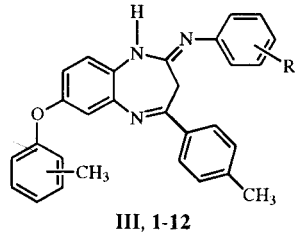
As a part of a program directed towards the synthesis and spectral property determination of 7-[(*o*-, *m*- and *p*-substituted)phenoxy]-1,5-benzodiazepine derivatives with possible pharmacological activity, we describe in this report the synthesis of the novel compounds 2,3-dihydro-2-[(*o*- and *p*-substituted)anilinylidene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines **III**, **1-12** (Scheme 1) as shown in Scheme 2.

Treatment of compounds **I**, with sodium hydride and methyl iodide at reflux in anhydrous *ortho*-xylene for five hours afforded compounds 2-methylthio-3*H*-4-(*para*-methylphenyl)-7-(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines **II**, in 84-88% yield.

A mixture of 0.001 mole of compounds 2-methylthio **II**, 0.002 mole of the corresponding substituted-phenylamine in the presence of a few drops of acetic acid at reflux in anhydrous toluene for 24-48 hours [11], afforded the 2,3-dihydro-2-[(*o*- and *p*-substituted)anilinylidene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines **III**, **1-12** in 45-65% yields.

The infrared spectrum of compounds **1-12** displayed absorptions at 3434-3360 cm^{-1} for N-H stretching, at 1627-1656 cm^{-1} for C=N stretching, at 1246-1263 and 1350-1362 cm^{-1} for C-N stretching and at 1180-1228 cm^{-1} for C-O stretching and the corresponding absorptions for aromatic and R-substituents.

Scheme 1



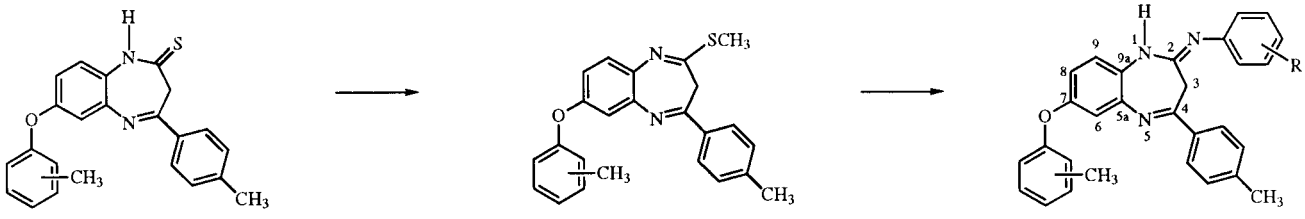
III, 1-12

	R	
1	*o*-CH_3	*p*-Cl
2	*o*-CH_3	*o*-Cl
3	*o*-CH_3	*p*-Br
4	*o*-CH_3	*o*-Br
5	*o*-CH_3	*p*-OCH_3
6	*o*-CH_3	*o*-OCH_3
7	*p*-CH_3	*p*-Cl
8	*p*-CH_3	*o*-Cl
9	*p*-CH_3	*p*-Br
10	*p*-CH_3	*o*-Br
11	*p*-CH_3	*p*-OCH_3
12	*p*-CH_3	*o*-OCH_3

In the ^{1}H nmr spectra the presence of three proton singlet signals at δ 2.20-2.35 were assigned to the methyl protons attached at phenyl of the "C" ring. The presence of three proton signals at δ 2.31-2.43 were assigned to the methyl protons attached at C-4" of the phenyl "D" ring. The presence of two broad proton signals at δ 4.20-4.63 was consistent with the methylene protons at C-3. The presence of a three proton multiplet signal at δ 6.43-7.14 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 6.83-7.75 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.

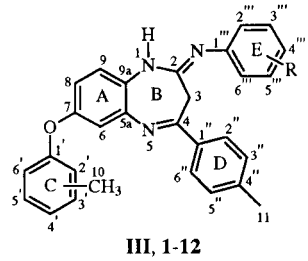
Scheme 2



I II III, 1-12

Table 1

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



III, 1-12

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3
R	*p*-Cl	*o*-Cl	*p*-Br	*o*-Br	*p*-OCH_3	*o*-OCH_3	*p*-Cl	*o*-Cl	*p*-Br	*o*-Br	*p*-OCH_3	*o*-OCH_3
C2	164.1	164.0	163.6	164.1	162.8	162.5	164.0	164.3	164.0	164.1	163.2	162.7
C3	39.5	39.4	39.6	39.5	39.5	39.6	39.5	39.6	39.5	39.6	39.4	39.5
C4	153.0	153.2	153.2	153.1	153.8	153.4	153.8	153.2	153.8	153.3	153.4	153.5
C5a	140.8	140.8	140.7	141.0	140.8	140.2	140.1	139.9	140.0	140.0	140.0	140.2
C6	111.1	111.0	111.3	111.2	111.2	111.1	111.7	112.2	112.8	112.0	112.0	111.5
C7	156.0	155.8	156.0	155.8	156.3	155.9	154.7	155.9	156.5	154.7	155.9	155.4
C8	113.8	114.0	114.1	114.0	114.6	113.9	115.2	114.8	115.4	115.0	114.2	114.8
C9	124.0	123.5	123.6	123.3	124.1	124.6	124.4	123.6	123.8	123.9	122.5	123.6
C9a	136.5	136.0	136.3	136.0	136.2	136.7	136.5	136.8	136.8	136.9	136.0	136.1
C1'	161.8	162.7	161.4	162.7	162.6	162.0	160.9	162.6	162.4	162.3	160.3	162.5
C2'	126.1	125.5	125.3	125.5	125.8	125.0	119.2	118.7	119.1	119.1	118.6	118.4
C3'	126.8	126.7	131.6	129.6	129.6	129.6	130.4	129.8	127.1	129.9	127.1	129.7
C4'	124.0	123.8	124.6	123.9	124.2	124.5	132.9	132.2	132.7	132.9	132.7	132.6
C5'	126.8	128.7	127.6	128.7	128.5	127.6	130.4	129.8	127.1	129.9	127.1	129.7
C6'	119.3	119.1	119.7	119.2	119.6	119.8	119.2	118.7	119.1	119.1	118.6	118.4
C1"	132.1	132.2	132.1	133.7	132.3	132.9	134.2	132.1	133.9	132.4	132.7	132.1
C2", C6"	129.1	128.7	132.6	132.9	131.6	131.6	128.0	127.2	132.6	132.6	129.8	126.8
C3", C5"	128.8	127.1	129.2	129.6	129.8	129.2	129.4	128.8	129.8	128.9	128.8	128.7
C4"	142.1	142.0	142.4	142.0	142.9	142.2	141.5	142.1	142.5	142.0	141.8	141.8
C1"'	132.8	132.2	132.8	132.3	126.2	128.4	132.9	132.7	134.5	131.1	126.0	126.1
C2"'	127.5	125.5	127.6	121.5	128.0	153.4	127.1	125.6	128.0	123.3	127.0	153.5
C3"'	131.0	129.3	129.1	128.7	114.6	112.8	129.1	129.5	130.4	129.2	114.2	112.0
C4"'	133.4	130.9	119.5	130.9	159.1	129.6	131.5	129.8	121.2	128.0	158.4	129.2
C5"'	131.0	128.9	129.1	127.8	114.6	120.9	129.2	130.0	130.4	129.8	114.2	119.2
C6"'	127.1	127.3	127.6	126.7	128.0	128.5	129.1	129.3	128.0	127.6	127.0	128.9
C10	15.5	15.5	15.7	15.5	15.5	15.7	20.7	20.7	20.7	20.4	20.1	20.1
C11	20.9	20.8	20.9	20.8	20.8	20.9	21.4	21.4	21.4	21.3	20.8	20.8
R	—	—	—	—	55.5	56.0	—	—	—	—	55.0	55.3

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

The mass spectra of compounds **1-12** include ions at m/z ion molecular $[M]^+$ is the base peak when the R-substituent is attached in the *para*-position; $[M-1]^+$, $[M-15]^+$, $[M-R]^+$ is the base peak when R-substituent is attached in the *ortho*-position; $[M-40]^+$, $[116+R]^+$, m/z 339, 315, 314, 223, 208, 195 and 91.

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

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer. The ^1H 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 Uniti Plus-500 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 Jeol JMS-AX505 and on a 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 70eV.

General Procedure for the Synthesis of the 2,3-Dihydro-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1*H*-1,5-benzodiazepine-2-thiones **I** [3,4].

A mixture of 0.01 mole of 3,4-diaminophenylmethylphenyl ether, 0.01 mole of 3,3-dimercapto-1-(*p*-methylphenyl)-2-propen-1-one, in 100 ml of dry *ortho*-xylene was heated at reflux for eight hours. After cooling the crystals were collected and washed with hexane to yield compounds **I** in 60-65% yields.

General Procedure for the Synthesis of the 2-Methylthio-3*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines **II**.

A mixture of 0.007 mole of 1*H*-1,5-benzodiazepine-2-thione **I** and 0.021 mole of sodium hydride in 100 ml of dry *ortho*-xylene was heated at reflux for one hour. After the reaction mixture was cooled to room temperature, subsequently was added dropwise over a few minutes 0.021 mole of methyl iodide and the reflux was continued for five hours. 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 a semisolid, compound **II** in 84-88% yield.

General Procedure for the Synthesis of 2,3-Dihydro-2-[(*o*- and *p*-substituted)anilinylidene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*- and *p*-methyl)phenoxy]-1,5-benzodiazepines **III**, **1-12**.

To a stirred solution of 2-methylthio-1,5-benzodiazepine **II** (0.001 mole) in dry toluene (50 ml) at reflux, a solution of the corresponding *o*- and *p*-substituted-aniline (0.002 mole) in the same solvent (5.0 ml) was added dropwise over a few minutes. Subsequently four drops of acetic acid was added and reflux was continued for 24-48 hours. The reaction mixture was cooled to room temperature, washed with 50 ml of water, dried (sodium sulfate) and evaporated *in vacuo* to yield a semisolid. The residual semisolid was purified by crystallization from hexane-chloroform to yield compounds **III**, **1-12** (45-65%).

2,3-Dihydro-2-(*p*-chloroanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*o*-methylphenoxy)-1,5-benzodiazepine (**1**).

This compound was obtained as orange needles in 65% yield, mp 142°; ir (nujol mull): ν N-H 3414, C=N 1638, C-N 1356 and 1254, C-O 1225 and 1186 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.22 (s, 3H, $C_{2'}$-CH_3), 2.40 (s, 3H, $C_{4''}$-CH_3), 4.51 (bs, 2H, 3-H), 6.47 (d, d, 1H, J = 2.7, 8.4 Hz, 8-H), 6.60 (d, 1H, J = 2.7 Hz, 6-H), 6.92 (d, d, 1H, J = 1.5, 7.5 Hz, 6'-H), 7.01 (d, 1H, J = 8.4 Hz, 9-H), 7.09 (d, t, 1H, J = 1.5, 7.5 Hz, 4'-H), 7.18 (d, d, 1H, J = 1.8, 8.0 Hz, 3'-H), 7.22 (d, t, 1H, J = 1.8, 7.5 Hz, 5'-H), 7.23 and 7.40 (AA' BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 7.24 and 7.26 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "E" ring), 10.97 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 465 (M^+), 467 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}ClN_3O$: C, 74.75; H, 5.19, N, 9.02. Found: C, 74.64; H, 5.12; N, 9.11.

2,3-Dihydro-2-(*o*-chloroanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*o*-methylphenoxy)-1,5-benzodiazepine (**2**).

This compound was obtained as brownish needles in 50% yield, mp 194°; ir (nujol mull): ν N-H 3380, C=N 1650, C-N 1360 and 1254, C-O 1226 and 1187 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.21 (s, 3H, $C_{2'}$-CH_3), 2.40 (s, 3H, $C_{4''}$-CH_3), 4.23 (bs, 2H, 3-H), 6.46 (d, d, 1H, J = 2.5, 8.6 Hz, 8-H), 6.61 (d, 1H, J = 2.6 Hz, 6-H), 6.92 (d, 1H, J = 8.4 Hz, 9-H), 7.01 (d, d, 1H, J = 1.5, 7.5 Hz, 6'-H), 7.09 (d, t, 1H, J = 1.5, 7.2 Hz, 4'-H), 7.17 (d, t, 1H, J = 1.5, 8.1 Hz, 5'-H), 7.19 and 7.23 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 7.23 (d, d, 1H, J = 1.5, 7.5 Hz, 3'-H), 7.24 (d, t, 1H, J = 1.5, 7.0 Hz, 4'''-H), 7.32 (d, d, 1H, J = 1.5, 7.1 Hz, 3'''-H), 7.35 (d, t, 1H, J = 1.5, 7.0 Hz, 5'''-H), 7.52 (d, d, 1H, J = 1.5, 7.0 Hz, 6'''-H), 10.94 (bs, 1H, -NH, deuterium oxide exchangeable); ms: m/z 465 (M^+), 467 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}ClN_3O$: C, 74.75; H, 5.19; N, 9.02. Found: C, 74.86; H, 5.26; N, 9.09.

2,3-Dihydro-2-(*p*-bromoanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*o*-methylphenoxy)-1,5-benzodiazepine (**3**).

This compound was obtained as orange needles in 65% yield, mp 152°; ir (nujol mull): ν N-H 3343, C=N 1638, C-N 1357 and 1258, C-O 1226 and 1187 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.22 (s, 3H, $C_{2'}$-CH_3), 2.43 (s, 3H, $C_{4''}$-CH_3), 4.60 (bs, 2H, 3-H), 6.62 (d, d, 1H, J = 2.7, 8.7 Hz, 8-H), 6.71 (d, 1H, J = 2.4 Hz, 6-H), 6.92 (d, 1H, J = 8.1 Hz, 9-H), 6.96 (d, d, 1H, J = 1.8, 7.5 Hz, 6'-H), 7.13 (d, t, 1H, J = 1.5, 7.5 Hz, 4'-H), 7.21 (d, t, 1H, J = 1.5, 7.8 Hz, 5'-H), 7.22 and 7.33 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "E" ring), 7.23 and 7.39 Hz (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.30 (d, d, 1H, J = 1.8, 7.8 Hz,

3'-H), 10.95 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 509 (M^+); 511 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}BrN_3O$: C, 68.24; H, 4.74; N, 8.23. Found: C, 68.14; H, 4.81; N, 8.17.

2,3-Dihydro-2-(*o*-bromoanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*o*-methylphenoxy)-1,5-benzodiazepine (**4**).

This compound was obtained as brownish needles in 52% yield, mp 144°; ir (nujol mull): ν N-H 3375, C=N 1645, C-H 1360 and 1258, C-O 1226 and 1186 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.20 (s, 3H, $C_{2'}$-CH_3), 2.41 (s, 3H, $C_{4''}$-CH_3), 4.23 (bs, 2H, 3-H), 6.47 (d, d, 1H, J = 2.5, 8.7 Hz, 8-H), 6.63 (d, 1H, J = 2.7 Hz, 6-H), 6.92 (d, 1H, J = 7.8 Hz, 9-H), 6.98 (d, d, 1H, J = 1.8, 7.8 Hz, 6'-H), 7.09 (d, t, 1H, J = 1.5, 7.5 Hz, 4'-H), 7.16 and 7.28 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 7.22 (d, t, 1H, J = 1.2, 7.5 Hz, 5'-H), 7.23 (d, t, 1H, J = 1.5, 7.5 Hz, 4'''-H), 7.24 (d, d, 1H, J = 1.8, 7.5 Hz, 3'-H), 7.25 (d, t, 1H, J = 1.5, 7.4 Hz, 5'''-H), 7.26 (d, d, 1H, J = 1.5, 7.5 Hz, 3'''-H), 7.33 (d, d, 1H, J = 1.7, 7.7 Hz, 6'''-H), 10.86 (bs, 1H, N-H, deuterium oxide exchangeable); ms: m/z 509 (M^+), 511 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}BrN_3O$: C, 68.24; H, 4.74; N, 8.23. Found: C, 68.35; H, 4.62; N, 8.32.

2,3-Dihydro-2-(*p*-methoxyanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*o*-methylphenoxy)-1,5-benzodiazepine (**5**).

This compound was obtained as yellow needles in 55% yield, mp 140°; ir (nujol mull): ν N-H 3360, C=N 1646, C-N 1359 and 1249, C-O 1226 and 1185 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.20 (s, 3H, $C_{2'}$-CH_3), 2.31 (s, 3H, $C_{4''}$-CH_3), 3.83 (s, 3H, $C_{4'''}$-OCH_3), 4.52 (bs, 2H, 3-H), 6.43 (d, d, 1H, J = 2.4, 8.7 Hz, 8-H), 6.60 (d, 1H, J = 2.4 Hz, 6-H), 6.90 (d, 1H, J = 7.5 Hz, 9-H), 6.90 and 7.13 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "E" ring), 6.99 (d, d, 1H, J = 1.8, 8.1 Hz, 6'-H), 7.05 (d, t, 1H, J = 1.5, 7.8 Hz, 4'-H), 7.16 and 7.32 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 7.19 (d, t, 1H, J = 1.2, 7.5 Hz, 5'-H), 7.23 (d, d, 1H, J = 1.8, 7.5 Hz, 3'-H), 10.94 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 461 (M^+).

Anal. Calcd. for $C_{30}H_{27}N_3O_2$: C, 78.06; H, 5.90; N, 9.11. Found: C, 78.16; H, 5.99; N, 9.21.

2,3-Dihydro-2-(*o*-methoxyanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*o*-methylphenoxy)-1,5-benzodiazepine (**6**).

This compound was obtained as brownish needles in 50% yield, mp 145°; ir (nujol mull): ν N-H 3401, C=N 1645, C-N 1350 and 1263, C-O 1228 and 1184 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.21 (s, 3H, $C_{2'}$-CH_3), 2.43 (s, 3H, $C_{4''}$-CH_3), 3.95 (s, 3H, $C_{2'''}$-OCH_3), 4.63 (bs, 2H, 3-H), 6.60 (d, d, 1H, J = 2.7, 8.7 Hz, 8-H), 6.71 (d, 1H, J = 2.7 Hz, 6-H), 6.96 (d, 1H, J = 7.8 Hz, 9-H), 6.97 (d, d, 1H, J = 1.8, 7.5 Hz, 6'-H), 7.07 (d, d, 1H, J = 1.8, 7.8 Hz, 3'''-H), 7.13 (d, t, 1H, J = 1.5, 7.8 Hz, 4'-H), 7.14 (d, t, 1H, J = 1.5, 7.5 Hz, 5'''-H), 7.18 and 7.33 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "D" ring), 7.22 (d, t, 1H, J = 1.5, 8.1 Hz, 4'''-H), 7.29 (d, d, 1H, J = 1.8, 7.5 Hz, 6'''-H), 7.30 (d, d, 1H, J = 1.8, 7.8 Hz, 3'-H), 7.31 (d, t, 1H, J = 1.2, 7.5 Hz, 5'-H), 10.90 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 461 (M^+).

Anal. Calcd. for $C_{30}H_{27}N_3O_2$: C, 78.06; H, 5.90; N, 9.11. Found: C, 78.14; H, 5.82; N, 9.01.

2,3-Dihydro-2-(*p*-chloroanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*p*-methylphenoxy)-1,5-benzodiazepine (**7**).

This compound was obtained as brown needles in 65% yield, mp 128°; ir (nujol mull): ν N-H 3414, C=N 1627, C-N 1350 and 1246, C-O 1210 and 1175 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.31 (s, 3H, $C_{4'}$-CH_3), 2.40 (s, 3H, $C_{4''}$-CH_3), 4.62 (bs, 2H, 3-H), 6.58 (d, d, 1H, J = 2.7, 8.7 Hz, 8-H), 6.80 (d, 1H, J = 2.7 Hz, 6-H), 6.90 (d, 1H, J = 8.1 Hz, 9-H), 6.96 and 7.13 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "C" ring), 7.13 and 7.29 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "E" ring), 7.19 and 7.45 (AA'BB', 4H, J = 7.8 Hz, phenyl protons of "D" ring), 10.82 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 465 (M^+); 467 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}ClN_3O$: C, 74.75; H, 5.19; N, 9.02. Found: C, 74.62; H, 5.10; N, 8.95.

2,3-Dihydro-2-(*o*-chloroanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*p*-methylphenoxy)-1,5-benzodiazepine (**8**).

This compound was obtained as red needles in 60% yield, mp 178°; ir (nujol mull): ν N-H 3425, C=N 1653, C-N 1362 and 1257, C-O 1215 and 1180 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.32 (s, 3H, $C_{4'}$-CH_3), 2.40 (s, 3H, $C_{4''}$-CH_3), 4.52 (bs, 2H, 3-H), 6.58 (d, d, 1H, J = 2.4, 8.4 Hz, 8-H), 6.74 (d, 1H, J = 2.4 Hz, 6-H), 6.84 (d, 1H, J = 8.4 Hz, 9-H), 6.92 and 7.18 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "C" ring), 7.14 (d, t, 1H, J = 1.8, 7.5 Hz, 4'''-H), 7.15 (d, t, 1H, J = 1.8, 7.4 Hz, 5'''-H), 7.16 (d, d, 1H, J = 1.8, 7.5 Hz, 3'''-H), 7.22 and 7.36 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 7.28 (d, d, 1H, J = 1.8, 7.5 Hz, 6'''-H), 10.90 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 465 (M^+); 467 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}ClN_3O$: C, 74.75; H, 5.19; N, 9.02. Found: C, 74.69; H, 5.27; N, 8.90.

2,3-Dihydro-2-(*p*-bromoanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*p*-methylphenoxy)-1,5-benzodiazepine (**9**).

This compound was obtained as brownish needles in 50% yield, mp 136°; ir (nujol mull); ν N-H 3392, C=N 1639, C-N 1356 and 1253, C-O 1213 and 1180 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.35 (s, 3H, $C_{4'}$-CH_3), 2.38 (s, 3H, $C_{4''}$-CH_3), 4.50 (bs, 2H, 3-H), 6.48 (d, d, 1H, J = 2.4, 8.1 Hz, 8-H), 6.81 (d, 1H, J = 2.4 Hz, 6-H), 6.83 and 7.12 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "C" ring), 6.90 (d, 1H, J = 8.1 Hz, 9-H), 7.18 and 7.24 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "E" ring), 7.27 and 7.41 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "D" ring), 10.83 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 509 (M^+), 511 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}BrN_3O$: C, 68.24; H, 4.74; N, 8.23. Found: C, 68.35; H, 4.64; N, 8.11.

2,3-Dihydro-2-(*o*-bromoanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*p*-methylphenoxy)-1,5-benzodiazepine (**10**).

This compound was obtained as brownish needles in 45% yield, mp 142°; ir (nujol mull): ν N-H 3420, C=N 1638, C-N 1358 and 1250, C-O 1213 and 1180 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.33 (s, 3H, $C_{4'}$-CH_3), 2.41 (s, 3H, $C_{4''}$-CH_3), 4.60 (bs, 2H, 3-H), 6.59 (d, d, 1H, J = 2.4, 8.4 Hz, 8-H), 6.80 (d, 1H, J = 2.7 Hz, 6-H), 6.93 (d, 1H, J = 8.4 Hz, 9-H), 6.95 and 7.19 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "C" ring), 7.18 (d, d, 1H, J = 1.8, 8.1 Hz, 3'''-H), 7.20 (d, t, 1H, J = 1.8, 8.1 Hz, 4'''-H), 7.21 (d, t, 1H, J = 1.5, 8.1 Hz, 5'''-H), 7.22 and 7.36 (AA'BB", 4H, J = 8.1 Hz, phenyl protons of "D" ring), 7.28 (d, d, 1H, J = 1.8, 7.8 Hz, 6'''-H), 10.93 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 509 (M^+); 511 $[M+2]^+$.

Anal. Calcd. for $C_{29}H_{24}BrN_3O$: C, 68.24; H, 4.74; N, 8.23. Found: C, 68.36; H, 4.83; N, 8.34.

2,3-Dihydro-2-(*p*-methoxyanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*p*-methylphenoxy)-1,5-benzodiazepine (**11**).

This compound was obtained as brown needles in 55% yield, mp 176°; ir (nujol mull): ν N-H 3405, C=N 1642, C-N 1360 and 1250, C-O 1213 and 1180 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.31 (s, 3H, $C_{4'}$-CH_3), 2.42 (s, 3H, $C_{4''}$-CH_3), 3.83 (s, 3H, $C_{4'''}$-OCH_3), 4.41 (bs, 2H, 3-H), 6.57 (d, d, 1H, J = 2.5, 8.5 Hz, 8-H), 6.74 (d, 1H, J = 2.4 Hz, 6-H), 6.90 (d, 1H, J = 8.1 Hz, 9-H), 6.91 and 7.17 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "C" ring), 6.98 and 7.21 (AA'BB', 4H, J = 8.7 Hz, phenyl potons of "E" ring), 7.19 and 7.32 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "D" ring), 10.86 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 461 (M^+).

Anal. Calcd. for $C_{30}H_{27}N_3O_2$: C, 78.06; H, 5.90; N, 9.11. Found: C, 78.19; H, 5.79; N, 9.04.

2,3-Dihydro-2-(*o*-methoxyanilinylidene)-1*H*-4-(*p*-methylphenyl)-7-(*p*-methylphenoxy)-1,5-benzodiazepine (**12**).

This compound was obtained as brown needles in 50% yield, mp 179°; ir (nujol mull): ν N-H 3420, C=N 1656, C-N 1360 and 1261, C-O 1214 and 1180 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.30 (s, 3H, $C_{4'}$-CH_3), 2.38 (s, 3H, $C_{4''}$-CH_3), 3.91 (s, 3H, $C_{2'''}$-OCH_3), 4.43 (bs, 2H, 3-H), 6.53 (d, d, 1H, J = 2.7, 8.7 Hz, 8-H), 6.59 (d, d, 1H, J = 1.8, 8.7 Hz, 3'''-H), 6.69 (d, 1H, J = 2.4 Hz, 6-H), 6.90 and 7.15 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "C" ring), 6.95 (d, 1H, J = 8.4 Hz, 9-H), 7.07 (d, t, 1H, J = 1.2, 8.5 Hz, 5'''-H), 7.14 (d, t, 1H, J = 1.5, 8.7 Hz, 4'''-H), 7.16 and 7.33 (AA'BB', 4H, J = 8.1 Hz, phenyl protons of "D" ring), 7.24 (d, d, 1H, J = 1.5, 8.7 Hz, 6'''-H), 10.91 (bs, 1H, NH, deuterium oxide exchangeable); ms: m/z 461 (M^+).

Anal. Calcd. for $C_{30}H_{27}N_3O_2$: C, 78.06; H, 5.90; N, 9.11. Found: C, 77.96; H, 5.80; N, 9.21.

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REFERENCES AND NOTES

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[3] E. Cortés C. and M. Martínez T., *J. Heterocyclic Chem.*, **34**, 953 (1997).

[4] E. Cortés C. and C. M. Alcocer C., *J. Heterocyclic Chem.* **34**, 1809 (1977).

[5] E. Cortés C., M. I. Becerra L. and Y. M. Osornio P., *J. Heterocyclic Chem.* **34**, 1833 (1997).

[6] E. Cortés C., O. García M. and E. Hernández C., *J. Heterocyclic Chem.*, submitted, 1998.

[7] H. L. Sterbach, *J. Med. Chem.*, **22**, 1 (1979).

[8] M. Cohen, *Ann. Rep. Ind. Med. Chem.*, **10**, 30 (1973).

[9] A. Chimirri, R. Giotto, S. Grasso, G. Romeo and M. Zappala, *Heterocycles*, **36**, 601 (1993).

[10] G. B. de Sarro, M. Zappala, S. Grasso, A. Chimirri, C. Spagnolo and A. de Sarro, *Mol. Neuropharmacol.*, **1**, 195 (1992).

[11] E. Cortés C., E. Cortés R. and A. Domínguez T., *J. Heterocyclic Chem.*, **31**, 725 (1994).