Synthesis and Spectral Determination of New Derivatives of 1-[(*p*-Substituted)phenyl]-3a-[(*o*- and *p*-substituted)phenyl]-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]benzodiazepines

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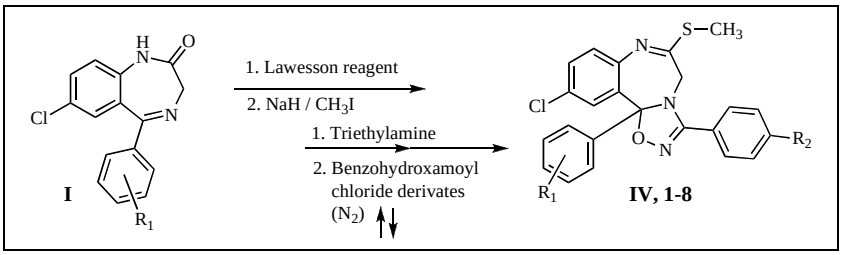

A new synthesis to obtain eight novel derivatives of 1-[(*p*-substituted)phenyl]-3a-[(o- and *p*-substituted)-phenyl]-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]benzodiazepines with possible biological and pharmacological activity as anxiolytics, hypnotics, anticonvulsants in the central nervous system. The final products were obtained by condensation between 2-methylthio-5-[(*o*-; *p*-substituted)-phenyl]-3*H*-7-chloro-[1,4]benzodiazepine with benzonitrile oxide generated *in situ* from benzohydroxamoyl chloride in triethylamine. The structure of all products was corroborated by ir, ^{1}H-nmr, ^{13}C-nmr, with experiments bidimensional and ms in low and high resolution.

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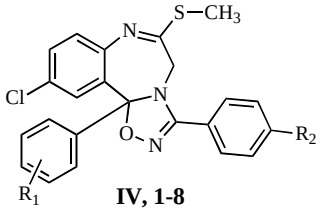
INTRODUCTION

The synthesis of benzodiazepinic derivatives with heterocyclic rings annelated to the “a”, “c” or “d” side [3-9] of the heptatomic system has recently attracted the interest of several researchers. The fusion of a heterocyclic system to the benzodiazepine ring appears, in fact, especially promising for the synthesis of derivates with greater activity and specificity and they show similar pharmacological profiles to the benzodiazepines from which they are obtained [10-12].

RESULTS AND DISCUSSION

We describe in this research report the synthesis of eight new derivatives and spectral properties of 1-[(p-substituted)phenyl]-3a-[(*o*- and *p*-substituted)phenyl]-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo-[2,3-*b*][1,4]benzodiazepines **IV, 1-8** (Figure 1). The synthesis of these compounds was carried out as shown in Scheme 1. Compounds **I** and benzohydroxamoyl chloride **III** were obtained by following literature methods with modifications [13-14].



	R_1	R_2
1	o-Cl	-Cl
2	p-Cl	-Cl
3	o-F	-Cl
4	p-F	-Cl
5	o-Cl	-Br
6	p-Cl	-Br
7	o-F	-Br
8	p-F	-Br

Figure 1

Compound **II** was obtained by the reaction of derivates **I** with Lawesson's reagent at reflux in anhydrous toluene for two hours, after this time the reaction mixture was treated with sodium hydride and methyl iodide at reflux for five hours; the semisolid residue obtained was purified on a silica gel chromatography column and elution with hexane-ethyl acetate (95:5). The derivates **II** were obtained in a 60-70% yield.

The reaction of compound **II**, with a slight excess of benzonitrile oxide generated *in situ* from benzohydroxamoyl chloride **III**, and triethylamine, has been performed at reflux in chloroform under a nitrogen atmosphere for four hours, the semisolid obtained of the reaction mixture was purified on a silica gel chromatography column and elution with hexane-ethyl acetate (98:2). The oxadiazolo[2,3-*b*][1,4]benzodiazepines, **IV, 1-8** have been obtained in a 20-35% yield, all the compounds obtained are solid with defined melting points.

The infrared spectra of compounds **IV, 1-8** displayed absorptions at 1602-1608 cm^{-1} for C=N stretching; at 1361-1368 cm^{-1} for C-N stretching; at 1072-1096 cm^{-1} for C-O stretching and the corresponding absorption for aromatic and R-substituents.

In the ^{1}H-nmr spectra the presence of three proton signals at δ 2.1-2.3 singlet were assigned to the methyl protons joined to sulfur (S-CH_3). The presence of two proton signals at δ 3.5-3.6 and 3.9-4.2 doublet was consistent with the methylene protons of C-10. The presence of three protons signals at δ 6.97-7.93 multiplet

was assigned to the aromatic protons of C-4, C-6 and C-7 of the benzodiazepine framework. The other aromatic protons appear as a multiplet and AA'BB' systems at δ 6.64-7.64 and 7.42-7.65, for phenyl protons of "D" ring; 6.99-7.39 for phenyl protons of "E" ring.

The ^{13}C-nmr spectra of the compounds **IV, 1-8** are given in Table 1, and the signals were confirmed by using HETCOR; LONG RANGE HETCOR, FLOCK, COSY and NOESY nmr experiments operating at 300 and 500 MHz.

Scheme 1

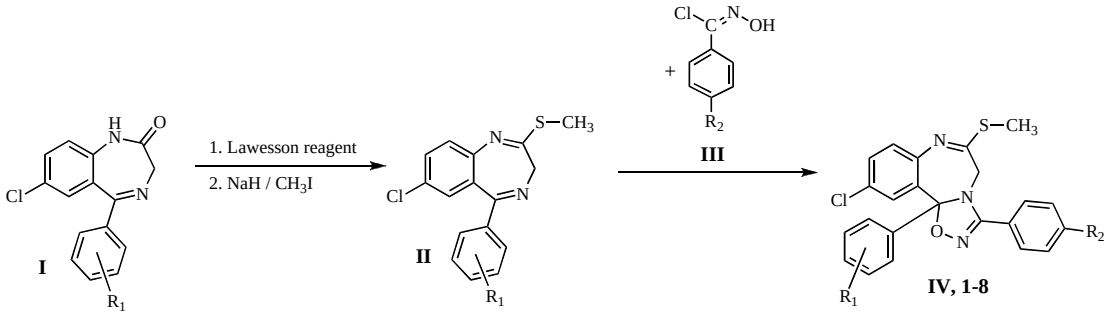
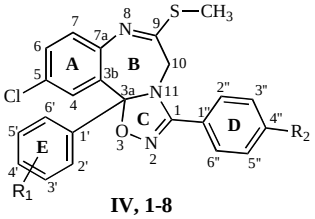


Table 1

^{13}C nmr Spectral data for compounds **IV, 1-8**



IV, 1-8

Compound	1	2	3	4	5	6	7	8
R_1	o-Cl	p-Cl	o-F	p-F	o-Cl	p-Cl	o-F	p-F
R_2	p-Cl	p-Cl	p-Cl	p-Cl	p-Br	p-Br	p-Br	p-Br
C-1	157.1	156.3	156.0	156.3	157.2	156.4	156.1	156.4
C-3a	102.0	100.8	99.9	100.9	102.0	100.8	100.0	100.9
C-3b	128.1	129.6	129.2	130.0	128.2	129.7	129.2	129.9
C-4	128.8	126.4	127.8	126.5	128.8	126.4	127.8	126.5
C-5	130.5	130.5	130.6	131.0	130.5	131.0	130.6	131.0
C-6	130.3	130.0	130.0	130.0	130.3	130.0	130.0	130.0
C-7	128.2	126.4	126.6	126.4	128.2	126.4	126.6	126.4
C-7a	145.9	143.2	143.8	143.3	145.9	143.2	143.8	143.3
C-9	168.4	166.9	166.1	165.4	168.4	165.5	166.1	165.4
C-10	48.8	48.5	48.2	48.5	48.8	48.5	48.2	48.5
C-1'	137.4	139.7	128.4 (d)	137.0 (d)	137.3	139.7	128.3 (d)	137.0 (d)
			$^2J_{C\text{-}F}$=9.0	$^4J_{C\text{-}F}$=3.3			$^2J_{C\text{-}F}$=11.7	$^4J_{C\text{-}F}$=3.0
C-2'	133.5	127.5	160.4 (d)	128.1 (d)	133.5	127.5	160.4 (d)	128.1 (d)
			$^1J_{C\text{-}F}$=249.1	$^3J_{C\text{-}F}$=8.2			$^1J_{C\text{-}F}$=251.5	$^3J_{C\text{-}F}$=8.2
C-3'	130.5	128.3	116.7 (d)	115.0 (d)	130.2	128.3	116.7 (d)	115.0 (d)
			$^2J_{C\text{-}F}$=23.0	$^2J_{C\text{-}F}$=21.8			$^2J_{C\text{-}F}$=23.0	$^2J_{C\text{-}F}$=21.9
C-4'	130.0	134.9	131.0 (d)	162.9 (d)	130.0	134.8	131.0 (d)	163.0 (d)
			$^3J_{C\text{-}F}$=6.9	$^1J_{C\text{-}F}$=246.7			$^3J_{C\text{-}F}$=9.2	$^1J_{C\text{-}F}$=247.3
C-5'	126.3	128.3	123.1 (d)	115.0 (d)	126.3	128.3	123.1 (d)	115.0 (d)
			$^4J_{C\text{-}F}$=5.8	$^2J_{C\text{-}F}$=21.8			$^4J_{C\text{-}F}$=4.5	$^2J_{C\text{-}F}$=21.9
C-6'	131.5	127.5	127.4 (d)	128.1 (d)	131.5	127.5	127.4 (d)	128.1 (d)
			$^3J_{C\text{-}F}$=3.7	$^3J_{C\text{-}F}$=8.2			$^3J_{C\text{-}F}$=3.2	$^3J_{C\text{-}F}$=8.2
C-1"	123.0	122.7	122.9	122.8	123.5	123.2	123.4	123.3
C-2"	129.7	129.6	129.5	129.6	132.3	132.5	132.4	132.6
C-3"	129.4	129.4	129.5	129.4	129.8	129.5	129.7	129.6
C-4"	137.4	137.5	137.4	137.5	125.8	125.8	125.8	125.8
C-5"	129.4	129.4	129.5	129.4	129.8	129.5	129.7	129.6
C-6"	129.7	129.6	129.5	129.6	132.3	132.5	132.4	132.6
S-CH_3	13.5	13.3	13.2	13.3	13.4	13.3	13.2	13.3

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

The mass spectra of the compounds **IV, 1-8** exhibit a stable molecular ion and the base peak is the [M-(76+R_1)] ion, in all the compounds analyzed. The main fragmentation was consistent with the assigned structures.

The relative abundance of the main fragmentation in the compounds **IV, 1-8** have some common features and the proposed fragmentation pathways leading to the formation of a number of important daughter ions have been confirmed by the corresponding parent ions spectra in Collision-Induced Dissociation experiments.

The elemental composition of the molecular ion and the other principal fragments ion was determined by exact mass measurements. The most important ion are: M^+; [M-(76+R_1)]$^+$ (base peak); [M-30] $^+$; [M-(133+R_2)] $^+$; [M-(119+R_2)] $^+$; [M-(118+R_2)] $^+$; [M-(118+ R_1+R_2)] $^+$; m/z [130+R_2] $^+$; m/z [104+R_1]$^+$; m/z [90+R_1]$^+$; m/z [76+R_1]$^+$; m/z [76+R_2]$^+$ and m/z 75.

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 spectrometer operating at 125 MHz in deuterochloroform 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-AC505 and JEOL MS-SX 102A high-resolution mass spectrometer with accurate mass determination of the molecular ion and the principal fragment 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.

The compounds **I** and **III** were prepared following methods developed by us, with modification [13-14].

General Procedure for the Synthesis of 7-Chloro-5-[(*o*-; *p*-substituted)phenyl]-3*H*-2-methylthio-[1,4]benzodiazepines II. Treatment of compounds [1,4]benzodiazepine-2-one **I,** (9.0 x 10^{-3} mole) with (4.5 x 10^{-3} mole) of Lawesson's reagent at reflux in anhydrous toluene under nitrogen atmosphere for two hours. After this time the reaction mixture was treated with sodium hydride (2.7 x 10^{-3} mole) and methyl iodide (2.7 x 10^{-3} mole) and the reflux under nitrogen atmosphere was continued for five hours. The reaction mixture was cooled to room temperature, filtered and the organic solution was dried with anhydrous sodium sulphate; filtered and evaporated in vacuum to yield a residual semisolid; and all these derivatives were purified on a silica gel chromatography column and elution with hexane-ethyl acetate (95:5) to yield the compounds **II** in a 60-70%.

General Procedure for the Synthesis 1-[(*p*-Substituted)-phenyl]-3a-[(*o*- and *p*-substituted)phenyl]-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]benzodiazepines IV, 1-8. To a stirred solution of 7-chloro-5-[(*o*-; *p*-substituted)phenyl]-3*H*-2-methylthio[1,4]benzodiazepines II, (0.55 x 10^{-3} mole) in dichloromethane (25.0 ml), a solution of triethylamine (1.1 x 10^{-3} mole) in the same solvent (2.0 ml) was added dropwise over a few minutes. The mixture was kept under a nitrogen atmosphere at reflux for one hour. Subsequently the reaction is cooled at room temperature and was added dropwise a solution of benzohydroxamoyl chloride derivates III, (1.1 x 10^{-3} mole) in dichloromethane (5.0 ml) and the reaction mixture was stirred and heated at reflux for two hours; followed by cooling to room temperature and the organic mixture was dried with anhydrous sodium sulphate and evaporated in vacuum to yield a semisolid. The residual semisolid was purified on a silica gel chromatography column and elution with hexane-ethyl acetate (98:2), to yield the compounds IV, 1-8 in a 20-35%.

1-(*p*-Chlorophenyl)-3a-(*o*-chlorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (1). This compound was obtained as an orange solid in a 34 % yield, mp 180 ºC; ir (chloroform): ν C=N 1609, C-N 1402 and 1364, S-CH_3 1267 and C-O 1094 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.36 (s, 3H, S-CH_3), 3.55 (d, 1H, J = 14.1 Hz, 10-H_b), 4.17 (d, 1H, J = 14.4 Hz, 10-H_a), 7.12 (d, 1H, J = 8.7 Hz, 7-H), 7.28 (dt, 1H, J = 1.8, 7.6 Hz, 5'-H), 7.31 (dd, 1H, J = 2.1, 7.5 Hz, 3'-H), 7.32 (dt, 1H, J = 1.8, 7.3 Hz, 4'-H), 7.38 (dd, 1H, J = 2.4, 8.7 Hz, 6'-H), 7.38 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 7.42 and 7.60 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "D" ring) and 7.81 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 487 (M^+); 489 [M+2]$^+$; 491 [M+4]$^+$; 493 [M+6]$^+$; 495 [M+8]$^+$. *Anal.* Calcd. for: $C_{23}H_{16}Cl_3N_3OS$: C, 56.51; H, 3.30; N, 8.60. Found: C, 56.59; H, 3.36; N, 8.50.

1-(*p*-Chlorophenyl)-3a-(*p*-chlorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (2). This compound was obtained as an orange solid in a 33% yield, mp 177ºC; ir (chloroform): ν C=N 1602, C-N 1400 and 1382, S-CH_3 1205 and C-O 1090 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.20 (s, 3H, SCH_3), 3.57 (d, 1H, J = 12.3 Hz, 10-H_b), 3.85 (d, 1H, J = 12.3 Hz, 10-H_a), 7.00 (d, 1H, J = 8.7 Hz, 7-H), 7.27 and 7.36 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "E" ring), 7.38 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 7.49 and 7.64 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "D" ring) and 7.92 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 487 (M^+); 489 [M+2]$^+$; 491 [M+4]$^+$; 493 [M+6]$^+$; 495 [M+8]$^+$. *Anal.* Calcd. for: $C_{23}H_{16}Cl_3N_3OS$: C, 56.51; H, 3.30; N, 8.60. Found: C, 56.42; H, 3.23; N, 8.67.

1-(*p*-Chlorophenyl)-3a-(*o*-fluorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (3). This compound was obtained as an orange solid in a 20% yield, mp 185ºC; ir (chloroform): ν C=N 1604, C-N 1406 and 1383, S-CH_3 1200 and C-O 1095 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.26 (s, 3H, S-CH_3), 3.39 (d, 1H, J = 13.2 Hz, 10-H_b), 3.60 (d, 1H, J = 12.9 Hz, 10-H_a), 6.99 (dd, 1H, J_{H-H} = 1.3, J_{H-H} = 8.1, J_{H-F}^1 = 11.7 Hz, 3'-H), 7.01 (d, 1H, J = 8.4 Hz, 7-H), 7.10 (dt, 1H, J_{H-H} =1.2, J_{H-H} = 7.6 Hz, 5'-H), 7.31 (dt, 1H, J_{H-H} = 1.8, J_{H-H} = 8.1, J_{H-F}^2 = 5.2 Hz, 4'-H), 7.36 (dd, 1H, J = 2.4, 8.7 Hz, 6-H), 7.47 and 7.63 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.64 (dd, 1H, J_{H-H} = 1.9, J_{H-H} = 7.5, J_{H-F}^2 = 5.7 Hz, 6'-H) and 7.79 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 471 (M^+); 473 [M+2]$^+$; 475 [M+4]$^+$; 477 [M+6]$^+$. *Anal.* Calcd. for: $C_{23}H_{16}Cl_2FN_3OS$: C, 58.48; H, 3.41; N, 8.90. Found: C, 58.40; H, 3.47; N, 8.99.

1-(*p*-Chlorophenyl)-3a-(*p*-fluorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (4). This compound was obtained as an orange solid in a 24% yield, mp 205ºC; ir (chloroform): ν C =N 1603, C-N 1406 and 1381, S-CH_3 1195 and C-O 1096 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.17 (s, 3H, S-CH_3), 3.56 (d, 1H, J = 12.3 Hz, 10-H_b), 3.85 (d, 1H, J = 12.3 Hz, 10-H_a), 6.97 (d, 1H, J = 8.7 Hz, 7-H), 6.99 (AA'BB', 2H, J_{H-H} = 8.7, J_{H-F}^1 = 12.3 Hz, phenyl protons, 3'-H and 5'-H of "E" ring), 7.39 (AA'BB', 2H,

J_{H-H} = 9.0, J_{H-F}^{2} = 5.1 Hz, phenyl protons, 2'-H and 6'-H of "C" ring), 7.36 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 7.49 and 7.64 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring) and 7.93 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 471 (M^+); 473 $[M+2]^+$; 475 $[M+4]^+$; 477 $[M+6]^+$. *Anal.* Calcd. for: $C_{23}H_{16}Cl_2FN_3OS$: C, 58.48; H, 3.41; N, 8.90. Found: C, 58.56; H, 3.34; N, 8.83.

1-(*p*-Bromophenyl)-3a-(*o*-chlorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (5). This compound was obtained as a scarlet solid in a 29% yield, mp 203ºC; ir (chloroform): ν C=N 1608, C-N 1400 and 1363, S-CH_3 1195 and C-O 1072 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.36 (s, 3H, S-CH_3), 3.55 (d, 1H, J = 13.8 Hz, 10-H_b), 4.17 (d, 1H, J = 14.4 Hz, 10-H_a), 7.12 (d, 1H, J = 8.7 Hz, 7-H), 7.27 (dt, 1H, J = 1.8, 7.1 Hz, 5'-H), 7.32 (dt, 1H, J = 2.1, 7.3 Hz, 4'-H), 7.33 (dd, 1H, J = 2.1, 7.2 Hz, 3'-H), 7.38 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 7.43 (dd, 1H, J = 1.8, 7.5 Hz, 6'-H), 7.52 and 7.58 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "D" ring) and 7.80 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 531 (M^+); 533 $[M+2]^+$; 535 $[M+4]^+$; 537 $[M+6]^+$; 539 $[M+8]^+$. *Anal.* Calcd. for: $C_{23}H_{16}BrCl_2N_3OS$: C, 51.80; H, 3.02; N, 7.88. Found: C, 51.71; H, 3.08; N, 7.97.

1-(*p*-Bromophenyl)-3a-(*p*-chlorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (6). This compound was obtained as a scarlet solid in a 35% yield, mp 158ºC; ir (chloroform): ν C=N 1609, C-N 1405 and 1380, S-CH_3 1205 and C-O 1077 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.19 (s, 3H, S-CH_3), 3.56 (d, 1H, J = 12.3 Hz, 10-H_b), 3.85 (d, 1H, J = 12.6 Hz, 10-H_a), 7.0 (d, 1H, J = 8.4 Hz, 7-H), 7.27 and 7.36 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "E" ring), 7.38 (dd, 1H, J = 2.4, 8.7 Hz, 6-H), 7.56 and 7.64 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring) and 7.91 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 531 (M^+); 533 $[M+2]^+$; 535 $[M+4]^+$; 537 $[M+6]^+$; 539 $[M+8]^+$. *Anal.* Calcd. for: $C_{23}H_{16}BrCl_2N_3OS$: C, 51.80; H, 3.02; N, 7.88. Found: C, 51.88; H, 3.09; N, 7.81.

1-(*p*-Bromophenyl)-3a-(*o*-fluorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (7). This compound was obtained as an orange solid in a 22% yield, mp 175ºC; ir (chloroform): ν C=N 1606, C-N 1404 and 1381, S-CH_3 1240 and C-O 1078 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.26 (s, 3H, S-CH_3), 3.59 (d, 1H, J = 13.2 Hz, 10-H_b), 3.93 (d, 1H, J = 12.9 Hz, 10-H_a), 6.84 (dd, 1H, J_{H-H} = 1.5, J_{H-H} = 8.2, J_{H-F}^{1} = 11.8 Hz, 3'-H), 7.02 (d, 1H, J = 8.7 Hz, 7-H), 7.10 (dt, 1H, J_{H-H} = 1.2, J_{H-H} = 7.5 Hz, 5'-H), 7.30 (dt, 1H, J_{H-H} = 1.8, J_{H-H} = 8.4, J_{H-F}^{2} = 5.4 Hz, 4'-H), 7.36 (dd, 1H, J = 2.3, 8.4 Hz, 6-H), 7.56 and 7.63 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring), 7.63 (dd, 1H, J_{H-H} = 1.8, J_{H-H} = 7.3, J_{H-F}^{2} = 6.0 Hz, 6'H) and 7.79 (d, 1H, J = 7.79 Hz, 4-H). ms: m/z 515 (M^+); 517 $[M+2]^+$; 519 $[M+4]^+$; 521 $[M+6]^+$. *Anal.* Calcd. for: $C_{23}H_{16}BrClFN_3OS$: C, 53.45; H, 3.12; N, 8.13. Found: C, 53.38; H, 3.17; N, 8.22.

1-(*p*-Bromophenyl)-3a-(*p*-fluorophenyl)-5-chloro-9-methylthio-10,3a-dihydro-[1,2,4]-oxadiazolo[2,3-*b*][1,4]-benzodiazepine (8). This compound was obtained as a scarlet solid in a 20% yield, mp 157ºC; ir (chloroform): ν C=N 1604, C-N 1404 and 1381, S-CH_3 1240 and C-O 1078 cm^{-1}; ^{1}H-nmr (deuterochloroform): δ 2.17 (s, 3H, S-CH_3), 3.55 (d, 1H, J = 12.3 Hz, 10-H_b), 3.84 (d,1H, J = 12.3 Hz, 10-H_a), 6.97 (d, 1H, J = 8.7 Hz, H-7), 6.99 (AA'BB', 2H, J_{H-H} = 8.7, J_{H-F}^{1} = 11.7 Hz, phenyl protons 3'-H and 5'-H of "C" ring), 7.39 (AA'BB', 2H, J_{H-H} = 9.1, J_{H-F}^{2} = 5.1 Hz, phenyl protons 2'-H and 6'-H of "C" ring), 7.39 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 7.57 and 7.65 (AA'BB', 4H, J = 8.7 Hz, phenyl protons of "D" ring) and 7.93 (d, 1H, J = 2.4 Hz, 4-H). ms: m/z 515 (M^+); 517 $[M+2]^+$; 519 $[M+4]^+$; 521 $[M+6]^+$. *Anal.* Calcd. for: $C_{23}H_{16}BrClFN_3OS$: C, 53.45; H, 3.12; N, 8.13. Found: C, 53.53; H, 3.06; N, 8.04.

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REFERENCES

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[3] J. B. Hester, A. D. Rudzik and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971); K. Meguro, H. Tawada, H. Miyano, Y. Sato and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 2382 (1973); A. Walser and G. Zenchoff, *J. Med. Chem.*, **20**, 1694 (1977).

[4] A. Gagneux, R. Heckendorn and R. Meier, German Offen., 2,304,307 (1973); *Chem. Abstr.*, **79**, 126535c (1973).

[5] D. L. Coffen, R. I. Fryer, D. A. Katonak and F. Wong, *J. Org. Chem.*, **40**, 894 (1975).

[6] N. W. Gillman, and R. I. Fryer, *J. Heterocyclic. Chem.*, **14**, 1171 (1977); R. B. Moffett, G. N. Evenson and P. F. Von Voigtander, *J. Heterocyclic. Chem.,* **14**, 1231 (1977); I. R. Ager, G. W. Danswan, D. R. Harrison, D. P. Kay, P. D. Kennewell, and J. B. Taylor, *J. Med. Chem.*, **20**, 1035 (1977); G. W. H Cheseman and S. G. Greenberg *J. Heterocyclic. Chem.*, **16**, 241 (1979).

[7] J. B. Hester, D. J. Duchamp and C. G. Chidester, *Tetrahedron Letters*, 1609 (1971).

[8] R. Madronero and S. Vega, *J. Heterocyclic Chem.*, **15**, 1127 (1978); P. C. Wade, B. R. Vogt, B. Toeplitz, M. S. Puar and J. Z. Gougoutas, *J. Org. Chem.*, **44**, 88 (1979); E. Aiello, G. Dattolo, G. Chirrincione, S. Plecia and G. Daidone, *J. Heterocyclic Chem.*, **16**, 209 (1979).

[9] E. Cortés Cortés, O. García Mellado and E. Hernández Cruz, *J. Heterocyclic Chem.*, **36**, 477 (1999).

[10] A. Chimirri, S. Grasso, R. Ottana, G. Romero and M. Zappala, *J. Heterocyclic Chem.*, **27**, 371 (1990).

[11] E. Cortés and A. M. Mendoza, *J. Heterocyclic Chem.*, **33**, 1159 (1996).

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

[13] E. Cortés Cortés, I. Ebromares, O. García Mellado, *J. Heterocyclic Chem.*, **39**, 1189 (2002).

[14] K. C. Liu, B.R. Shelton and R. K. Howe, *J. Org. Chem.*, **45**, 3916, (1980).