# Synthesis and Spectral Properties of 7-Chloro-5-[(*o*- and *p*-$R_1$)phenyl]-1-$R_2$-3*H*-[1,4]benzodiazepin-2-ones



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A series of twelve new 7-chloro-5-[(*o*- and *p*-$R_1$)phenyl]-1-$R_2$-3*H*-[1,4] benzo-diazepin-2-ones, which have possible pharmacological properties were synthesized. The synthesis of all the final compounds was carried out by four steps. The structure of all final products was corroborated by ir, $^1$H nmr, $^{13}$C nmr and ms, and have been obtained in 35-94% yield.

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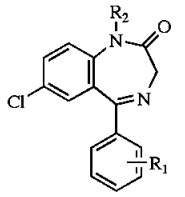
Benzodiazepines [3] have been an important pharmacophore in the pharmaceutical industry. The therapeutic applications of benzodiazepines include anxiolytics [4], hypnotic [5], antiarrhythmics [6], vasopressin antagonists [7], HIV reverse transcriptase inhibitors [8], and cholecystokinin antagonists [9]. The diazepam [10], flunitrazepam [11] and Lormetazepam [11] are [1,4]benzodiazepin-2-ones that have a methyl group on the amide nitrogen, these compounds are classified as anxiolytic and hypnotic. These benzodiazepines are depressant and act by binding at a receptor for the γ aminobutyric ($GABA_A$) in the brain [12]. At the moment there is considerable interest in the synthesis of new benzodiazepines with pharmacological activity. We have previously reported the synthesis of 2-[(*o*- and *p*-substituted) aminophenyl]-3*H*-5-[(*o*- and *p*-substituted)phenyl]-7-chloro-1,4-benzodiazepines [13], 2,3-dihydro-2-[*o*-; and *p*-substituted)anilinylidene]-1*H*-4-(*p*-methylphenyl)-7-[(*o*-; and *p*-methyl)phenoxy]-1,5-benzodiazepines [14] and 2-methylthio-3*H*-4-(*p*-substituted-phenyl)-7-[(*o*- and *p*-substituted)phenylthio]-1,5-benzodiazepines [15].

As a part of our program directed toward the synthesis and the spectral property determination of [1,4]benzodiazepine derivatives with possible pharmacological activity, we described in this report the synthesis of the novel compounds of 7-chloro-5-[(*o*- and *p*-$R_1$)phenyl]-1-$R_2$-3*H*-[1,4]benzodiazepin-2-ones **IV, 1-12** (Figure 1). The synthesis of these compounds was carried out by four steps as shown in Scheme 1. The synthesis route was proven with the diazepam, which was obtained in 80 % yield in the last step.

The reaction of *o*- and *p*-substituted-benzoyl chloride with *p*-chloroaniline and zinc chloride was heated at 220° for three hours. After 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); 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 40-47 %. Treatment of compounds **I** with bromoacetyl bromide in dry ether, with stirring at a constant temperature of 10° during two hours

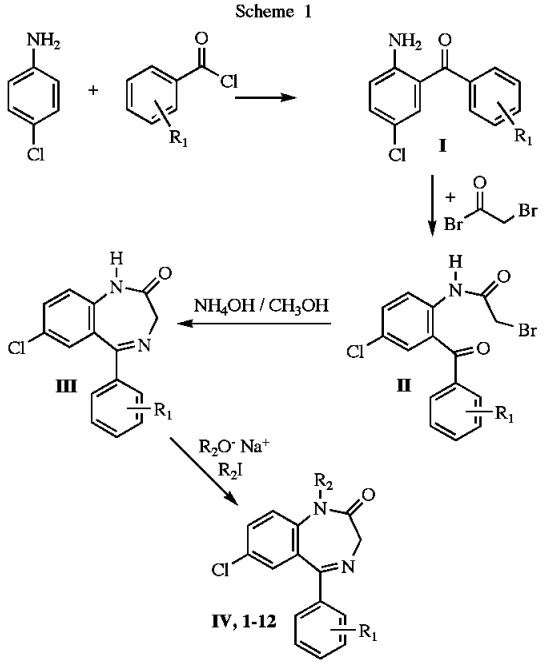


**IV, 1-12**

| | $R_1$ | $R_2$ |
|---|---|---|
| **1** | *o*-Cl | H |
| **2** | *o*-Cl | $CH_3$ |
| **3** | *o*-Cl | $CH_2CH_3$ |
| **4** | *p*-Cl | H |
| **5** | *p*-Cl | $CH_3$ |
| **6** | *p*-Cl | $CH_2CH_3$ |
| **7** | *o*-F | H |
| **8** | *o*-F | $CH_3$ |
| **9** | *o*-F | $CH_2CH_3$ |
| **10** | *p*-F | H |
| **11** | *p*-F | $CH_3$ |
| **12** | *p*-F | $CH_2CH_3$ |

Figure 1

Scheme 1



afforded the [2-bromoacetamide-5-chlorophenyl]-[(*o*- and *p*-$R_1$)phenyl] ketones **II**, in 94-98 % yield.

The ketone **II** was dissolved in dry ether, subsequently a mixture of ammonium hydroxide/methanol 20% was added and the reaction mixture was stirred to room temperature for 48 hours. The 7-chloro-5-[(*o*- and *p*-$R_1$)phenyl]-3*H*-[1,4]benzodiazepin-2-ones **III** have been obtained in 60-80 % yield.

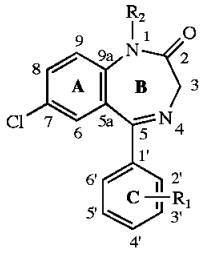
The 7-chloro-5-[(*o*- and *p*-$R_1$)phenyl]-3*H*-[1,4]benzodiazepin-2-ones **III** were dissolved in dry toluene and subsequently was added the corresponding sodium alkoxide and the reaction mixture was stirred at room temperature for thirty minutes after which was added the corresponding alkyl iodide. The reaction mixture was sealed tightly and was stirred to room temperature for seven days. The 7-chloro-5-[(*o*- and *p*-$R_1$)phenyl]-1-$R_2$-3*H*-[1,4]-benzodiazepines **IV, 1-12** have been obtained in 35-94 % yield.

The infrared spectrum of compounds **1-12** displayed absorptions at 1697-1674 $cm^{-1}$ for C=O stretching, at 1618-1599 $cm^{-1}$ for C=N stretching, at 1350-1321 and 1327-1300 $cm^{-1}$ for C-N stretching, at 1288-1130 and 1150-1094 $cm^{-1}$ for C-O stretching and the corresponding absorptions for aromatic and R-substituents. For the compounds **1**, **4**, **7** and **10** displayed absorptions at 3391-3398 $cm^{-1}$ for N-H stretching.

In the $^1$H-nmr spectra the presence of a doublet at δ 3.74-3.83 and 4.67-4.89 was consistent with the methylene protons at C-3, except for the compounds **1**, **4**, **7** and **10** the methylene protons at C-3 were a singlet signal at 4.20-4.40. The presence of a three proton multiplet signal at δ 7.02-7.60 was assigned to the aromatic protons at C-6, C-8 and C-9 of the benzodiazepine framework. The other aromatic protons appeared as a multiplet and an AA'BB' system at δ 7.06-7.66 and with the signal for the

Table 1

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




**IV, 1-12**

| Compounds | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_1$ | *o*-Cl | *o*-Cl | *o*-Cl | *p*-Cl | *p*-Cl | *p*-Cl | *o*-F | *o*-F | *o*-F | *p*-F | *p*-F | *P* -F |
| $R_2$ | H | $CH_3$ | $CH_2CH_3$ | H | $CH_3$ | $CH_2CH_3$ | H | $CH_3$ | $CH_2CH_3$ | H | $CH_3$ | $CH_2CH_3$ |
| C-2 | 171.3 | 169.3 | 168.6 | 169.8 | 169.7 | 168.4 | 171.3 | 169.3 | 168.1 | 172.0 | 168.8 | 168.5 |
| C-3 | 56.6 | 56.8 | 57.1 | 56.8 | 57.0 | 57.2 | 56.6 | 56.8 | 57.1 | 56.6 | 56.3 | 57.1 |
| C-5 | 169.4 | 168.2 | 168.2 | 167.5 | 167.7 | 167.6 | 166.6 | 165.9 | 165.8 | 168.6 | 166.8 | 167.6 |
| C-5a | 129.1 | 129.7 | 129.7 | 127.0 | 129.5 | 129.5 | 129.2 | 129.6 | 130.0 | 128.3 | 128.2 | 128.3 |
| C-6 | 129.2 | 128.0 | 128.2 | 129.3 | 129.7 | 129.5 | 129.3 | 128.4 | 128.2 | 130.5 | 129.0 | 129.8 |
| C-7 | 129.2 | 131.3 | 132.1 | 127.1 | 129.8 | 129.8 | 129.4 | 131.1 | 130.0 | 128.9 | 128.7 | 129.6 |
| C-8 | 131.9 | 131.5 | 131.5 | 131.2 | 131.8 | 131.6 | 131.9 | 131.5 | 131.4 | 131.9 | 131.1 | 131.5 |
| C-9 | 122.6 | 122.7 | 123.2 | 122.7 | 122.6 | 123.5 | 122.6 | 122.6 | 123.6 | 122.8 | 122.8 | 123.5 |
| C-9a | 138.3 | 141.9 | 140.5 | 137.0 | 137.0 | 137.0 | 136.3 | 141.3 | 139.8 | 137.4 | 142.0 | 141.2 |
| C-1' | 136.6 | 137.9 | 137.7 | 135.7 | 136.6 | 136.7 | 127.2 (d) | 126.6 (d) | 126.7 (d) | 134.9 (d) | 133.9 (d) | 134.5 (d) |
| | | | | | | | $^2J_{C-F}$=12.1 | $^2J_{C-F}$=12.1 | $^2J_{C-F}$=12.1 | $^4J_{C-F}$=3.3 | $^4J_{C-F}$=3.3 | $^4J_{C-F}$=3.3 |
| C-2' | 133.2 | 133.1 | 133.0 | 130.4 | 130.7 | 130.6 | 160.4 (d) | 160.4 (d) | 160.5 (d) | 131.6 (d) | 131.0 (d) | 131.3 (d) |
| | | | | | | | $^1J_{C-F}$=252.0 | $^1J_{C-F}$=251.9 | $^1J_{C-F}$=251.8 | $^3J_{C-F}$=8.8 | $^3J_{C-F}$=8.7 | $^3J_{C-F}$=7.7 |
| C-3' | 130.2 | 130.2 | 130.2 | 128.0 | 128.7 | 128.7 | 116.3 (d) | 116.2 (d) | 116.2 (d) | 115.4 (d) | 114.8 (d) | 115.5 (d) |
| | | | | | | | $^2J_{C-F}$=20.5 | $^2J_{C-F}$=22.0 | $^2J_{C-F}$=21.9 | $^2J_{C-F}$=22.0 | $^2J_{C-F}$=22.0 | $^2J_{C-F}$=21.9 |
| C-4' | 131.0 | 131.0 | 131.2 | 138.2 | 142.7 | 141.3 | 132.2 (d) | 132.4 (d) | 132.3 (d) | 164.3 (d) | 163.4 (d) | 166.4 (d) |
| | | | | | | | $^3J_{C-F}$=8.7 | $^3J_{C-F}$=7.7 | $^3J_{C-F}$=8.7 | $^1J_{C-F}$=250.0 | $^1J_{C-F}$=249.0 | $^1J_{C-F}$=250.0 |
| C-5' | 127.0 | 127.1 | 127.1 | 128.0 | 128.7 | 128.7 | 124.4 (d) | 124.5 (d) | 124.5 (d) | 115.4 (d) | 114.8 (d) | 115.5 (d) |
| | | | | | | | $^4J_{C-F}$=3.3 | $^4J_{C-F}$=3.2 | $^4J_{C-F}$=4.3 | $^2J_{C-F}$=22.0 | $^2J_{C-F}$=22.0 | $^2J_{C-F}$=21.9 |
| C-6' | 131.0 | 131.1 | 131.4 | 130.4 | 130.7 | 130.6 | 131.4 (d) | 131.2 (d) | 128.2 (d) | 131.6 (d) | 131.0 (d) | 131.3 (d) |
| | | | | | | | $^3J_{C-F}$=2.2 | $^3J_{C-F}$=2.2 | $^3J_{C-F}$=2.2 | $^3J_{C-F}$=8.8 | $^3J_{C-F}$=8.7 | $^3J_{C-F}$=7.7 |
| N-$CH_3$ | - | 34.8 | - | - | 34.8 | - | - | 34.9 | - | - | 34.1 | - |
| N- $CH_2CH_3$ | - | - | 42.2 | - | - | 42.3 | - | - | 42.1 | - | - | 42.2 |
| N- $CH_2CH_3$ | - | - | 13.7 | - | - | 13.4 | - | - | 13.0 | - | - | 13.4 |

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

R-substituents. The alkyl protons appeared upfield as a typical signal. For the compounds **1**, **4**, **7** and **10** the presence of a broad proton signal at δ 9.70-10.59 was consistent with N-H, deuterium oxide exchangeable.

The $^{13}$C-nmr spectra of compounds **1-12** are given in Table 1. The signals were confirmed by using HETCOR, long range HETCOR, FLOCK, COSY and NOESY nmr experiments operating at 300 and 500 MHz.

The mass spectra of compounds **1-12** include molecular ions $[M]^+$ that are the base peak when the $R_1$-substituent is attached in the *orto*-position; $[M-28]^+$ is the base peak when $R_1$-substituent is attached in the *para*-position. Other important fragments are: $[M-1]^+$, $[M-28]^+$, $[M-29]^+$, $[M-R_1]^+$, $[M-(28+R_1)]^+$, $[M-(28+R_2)]^+$, $[M-63]^+$, m/z 177, 165 and 75. 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 by the corresponding parent ion spectra in 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 $^1$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 deuteriochloroform 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 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**, **II** and **III** were prepared following literature methods with modifications [13].

General Procedure for the Synthesis of the 7-Chloro-5-[(*o*- and *p*-$R_1$)phenyl]-1-$R_2$-3*H*-[1,4]benzodiazepin-2-ones **IV**, **1-12**.

A two neck round bottom flask, 0.37 x $10^{-3}$ mole of 7-chloro-5-[(*o*- and *p*-$R_1$)phenyl]-3*H*-[1,4]benzodiazepin-2-one **III** was dissolved in 25 ml of dry toluene subsequently was added 1.9 x $10^{-3}$ mole of the corresponding sodium alkoxide recently prepared and the reaction mixture was stirred to room temperature for thirty minutes after which was added 1.1 x $10^{-3}$ mole of the corresponding alkyl iodide. The reaction mixture was sealed tightly and was stirred at room temperature for seven days. The reaction was monitored by thin layer chromatography until the end of the reaction, and the reaction mixture extracted with toluene and the organic phase was washed with water and dried over sodium sulfate, filtered and evaporated in *vacuo* to yield a solid or semisolid. The residual solid or semisolid was purified on a silica gel chromatography column and elution with hexane-ethyl acetate (98:2) to yield the compounds **IV, 1-12** (35-94 %).

7-Chloro-5-(*o*-chlorophenyl)-3*H*-[1,4]benzodiazepin-2-one (**1**).

This compound was obtained as a yellowish solid in 94% yield, mp 196°; ir (chloroform): ν N-H 3391, C=O 1693, C=N 1618, C-N 1325 and 1300, C-O 1253 and 1136 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 4.39 (bs, 2H, 3-H), 7.05 (d, 1H, J = 2.4 Hz, 6-H), 7.14 (d, 1H, J = 8.7 Hz, 9-H), 7.38 (dd, 1H, J = 2.0, 7.2 Hz, 3'-H), 7.39 (dt, 1H, J = 2.1, 6.3 Hz, 4'-H), 7.39 (dt, 1H, J = 2.1, 6.3 Hz, 5'-H), 7.42 (dd, 1H, J = 2.4, 8.6 Hz, 8-H), 7.52 (dd, 1H, J = 2.1, 7.4 Hz, 6'-H), 9.70 (bs, 1H, N-H) deuterium oxide exchangeable; ms: m/z 304 $(M)^+$, 306 $[M+2]^+$, 308 $[M+4]^+$.

*Anal.* Calcd. for: $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.11; H, 2.7; N, 9.23.

7-Chloro-5-(*o*-chlorophenyl)-1-methyl-3*H*-[1,4]benzodiazepin-2-one (**2**).

This compound was obtained as a yellow solid in 38% yield, mp 210°; ir (chloroform): ν C=O 1678, C=N 1616, C-N 1350 and 1323, C-O 1130 and 1120 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 3.43 (s, 3H, N-$CH_3$), 3.83 (d, 1H, J = 10.5 Hz, 3-$H_a$), 4.87 (d, 1H, J = 10.5 Hz, 3-$H_b$), 7.02 (d, 1H, J = 2.4 Hz, 6-H), 7.29 (d, 1H, J = 9.0 Hz, 9-H), 7.39 (dt, 1H, J = 2.1, 6.3 Hz, 5'-H), 7.41 (dd, 1H, J = 2.0, 7.2 Hz, 3'-H), 7.41 (dt, 1H, J = 2.0, 6.4 Hz, 4'-H), 7.48 (dd, 1H, J = 2.4, 8.8 Hz, 8-H), 7.59 (dd, 1H, J = 2.4, 7.9 Hz, 6'-H); ms: m/z 318 $(M)^+$, 320 $[M+2]^+$, 322 $[M+4]^+$.

*Anal.* Calcd. for: $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79; N, 8.78. Found: C, 60.14; H, 3.85; N, 8.72.

7-Chloro-5-(*o*-chlorophenyl)-1-ethyl-3*H*-[1,4]benzodiazepin-2-one (**3**).

This compound was obtained as a yellow semisolid in 35% yield; ir (chloroform): ν C=O 1676, C=N 1612, C-N 1321 and 1300, C-O 1269 and 1134 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 6.9 Hz, $CH_3$), 3.76 (q, 1H, J = 7.2 Hz, N-$CH_2$), 3.82 (d, 1H, J = 9.6 Hz, 3-$H_a$), 4.28 (q, 1H, J = 7.1 Hz, N-$CH_2$), 4.86 (d, 1H, J=9.6 Hz, 3-$H_b$), 7.03 (d, 1H, J = 2.4 Hz, 6-H), 7.30 (d, 1H, J = 8.7 Hz, 9-H), 7.39 (dt, 1H, J = 2.0, 6.4 Hz, 5'-H), 7.40 (dt, 1H, J = 1.8, 6.5 Hz, 4'-H), 7.41 (dd, 1H, J = 1.8, 7.2 Hz, 3'-H), 7.48 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.59 (dd, 1H, J = 2.4, 7.7 Hz, 6'-H); ms: m/z 332 $(M)^+$, 334 $[M+2]^+$, 336 $[M+4]^+$.

*Anal.* Calcd. for: $C_{17}H_{14}Cl_2N_2O$: C, 61.28; H, 4.23; N, 8.41. Found: C, 61.38; H, 4.29; N, 8.34.

7-Chloro-5-(*p*-chlorophenyl)-3*H*-[1,4]benzodiazepin-2-one (**4**).

This compound was obtained as a yellow solid in 80% yield, mp 210°; ir (chloroform): ν N-H 3391, C=O 1697, C=N 1610, C-N 1340 and 1321, C-O 1286 and 1157 $cm^{-1}$; $^1$H nmr (deuteriochloroform): δ 4.20 (bs, 2H, 3-H), 7.20 (d, 1H, J = 2.4 Hz, 6-H), 7.28 (d, 1H, J = 9.0 Hz, 9-H), 7.42 and 7.51 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "C" ring), 7.48 (dd, 1H, J = 2.4, 9.0 Hz, 8-H), 10.59 (bs, 1H, N-H) deuterium oxide exchangeable; ms: m/z 304 $(M)^+$, 306 $[M+2]^+$, 308 $[M+4]^+$.

*Anal.* Calcd. for: $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 59.12; H, 3.21; N, 9.12.

7-Chloro-5-(*p*-chlorophenyl)-1-methyl-3*H*-[1,4]benzodiazepin-2-one (**5**).

This compound was obtained as a yellowish solid in 37% yield, mp 210°; ir (chloroform): ν C=O 1678, C=N 1612, C-N 1350 and 1319, C-O 1130 and 1107 $cm^{-1}$; $^1$H nmr (deuteriochlo-

roform): δ 3.39 (s, 3H, N-$CH_3$), 3.76 (d, 1H, J = 11.1 Hz, 3-$H_a$), 4.83 (d, 1H, J = 11.1 Hz, 3-$H_b$), 7.26 (d, 1H, J = 2.7 Hz, 6-H), 7.31 (d, 1H, J = 9.0 Hz, 9-H), 7.39 and 7.56 (AA'BB', 4H, J = 8.4 Hz, phenyl protons of "C" ring), 7.53 (dd, 1H, J = 2.4, 9.0 Hz, 8-H); ms: m/z 318 $(M)^+$, 320 $[M+2]^+$, 322 $[M+4]^+$.

*Anal.* Calcd. for: $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.79; N, 8.78. Found: C, 60.10; H, 3.70; N, 8.86.

7-Chloro-5-(*p*-chlorophenyl)-1-ethyl-3*H*-[1,4]benzodiazepin-2-one (**6**).

This compound was obtained as a yellow semisolid in 45% yield; ir (chloroform): ν C=O 1678, C=N 1610, C-N 1321 and 1300, C-O 1267 and 1094 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.13 (t, 3H, J = 7.1 Hz, $CH_3$), 3.71 (q, 1H, J = 7.0 Hz, N-$CH_2$), 3.74 (d, 1H, J = 10.2 Hz, 3-$H_a$), 4.26 (q, 1H, J = 7.0 Hz, N-$CH_2$), 4.80 (d, 1H, J = 10.2 Hz, 3-$H_b$), 7.25 (d, 1H, J = 2.7 Hz, 6-H), 7.37 (d, 1H, J = 8.7 Hz, 9-H), 7.41 and 7.56 (AA'BB', 4H, J = 9.0 Hz, phenyl protons of "C" ring), 7.53 (dd, 1H J = 2.7, 9.0 Hz, 8-H); ms: m/z 332 $(M)^+$, 334 $[M+2]^+$, 336 $[M+4]^+$.

*Anal.* Calcd. for: $C_{17}H_{14}Cl_2N_2O$: C, 61.28; H, 4.23; N, 8.41. Found: C, 61.34; H, 4.30; N, 4.31.

7-Chloro-5-(*o*-fluorophenyl)-3*H*-[1,4]benzodiazepin-2-one (**7**).

This compound was obtained as a yellow solid in 89% yield, mp 200°; ir (chloroform): ν N-H 3391, C=O 1693, C=N 1614, C-N 1327 and 1300, C-O 1257 and 1150 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 4.40 (bs, 2H, 3-H), 7.08 (dd, 1H, $J_{H-H}$ = 0.9, $J_{H-H}$ = 8.4, $J_{H-F}^1$ = 9.6 Hz, 3'-H), 7.16 (d, 1H, J = 8.4 Hz, 9-H), 7.19 (d, 1H, J = 2.1 Hz, 6-H), 7.25 (dt, 1H, $J_{H-H}$ = 0.9, $J_{H-H}$ = 7.5 Hz, 5'-H), 7.44 (dd, 1H, J = 2.4, 8.4 Hz, 8-H), 7.46 (dt, 1H, $J_{H-H}$ = 2.1, $J_{H-H}$ = 8.4, $J_{H-F}^2$ = 5.4 Hz, 4'-H), 7.58 (dd, 1H, $J_{H-H}$ = 1.8, $J_{H-H}$ = 7.5, $J_{H-F}^2$ = 7.2 Hz, 6'-H), 9.83 (bs, 1H, N-H) deuterium oxide exchangeable; ms: m/z 288 $(M)^+$, 290 $[M+2]^+$.

*Anal.* Calcd. for: $C_{15}H_{10}ClFN_2O$: C, 62.40; H, 3.49; N, 9.71. Found: C, 62.32; H, 3.56; N, 9.77.

7-Chloro-5-(*o*-fluorophenyl)-1-methyl-3*H*-[1,4]benzodiazepin-2-one (**8**).

This compound was obtained as a yellow solid in 48% yield, mp 210°; ir (chloroform): ν C=O 1678, C=N 1614, C-N 1340 and 1327, C-O 1130 and 1105 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.42 (s, 3H, N-$CH_3$), 3.80 (d, 1H, J = 10.8 Hz, 3-$H_a$), 4.89 (d, 1H, J = 10.8 Hz, 3-$H_b$), 7.07 (dd, 1H, $J_{H-H}$ = 0.9, $J_{H-H}$ = 8.4, $J_{H-F}^1$ = 10.2 Hz, 3'-H), 7.17 (d, 1H, J = 2.4 Hz, 6-H), 7.26 (dt, 1H, $J_{H-H}$ = 1.2, $J_{H-H}$ = 7.8 Hz, 5'-H), 7.29 (d, 1H, J = 8.7 Hz, 9-H), 7.48 (dt, 1H, $J_{H-H}$ = 2.4, $J_{H-H}$ = 8.3, $J_{H-F}^2$ = 5.7 Hz, 4'-H), 7.49 (dd, 1H J = 2.5, 8.8 Hz, 8-H), 7.66 (dd, 1H, $J_{H-H}$ = 1.8, $J_{H-H}$ = 7.5, $J_{H-F}^2$ = 7.2 Hz, 6'-H); ms: m/z 302 $(M)^+$, 304 $[M+2]^+$.

*Anal.* Calcd. for: $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 3.99; N, 9.26. Found: C, 63.40; H, 4.05; N, 9.16.

7-Chloro-1-ethyl-5-(*o*-fluorophenyl)-3*H*-[1,4]benzodiazepin-2-one (**9**).

This compound was obtained as a yellow semisolid in 37% yield; ir (chloroform): ν C=O 1674, C=N 1614, C-N 1327 and 1300, C-O 1263 and 1105 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.11 (t, 3H, J = 7.1 Hz, $CH_3$), 3.67 (q, 1H, J = 7.2 Hz, N-$CH_2$), 3.77 (d, 1H, J = 10.5 Hz, 3-$H_a$), 4.39 (q, 1H, J = 7.1 Hz, N-$CH_2$), 4.85 (d, 1H, J = 10.5 Hz, 3-$H_b$), 7.06 (dd, 1H, $J_{H-H}$ = 0.6, $J_{H-H}$ = 8.7, $J_{H-F}^1$ = 9.3 Hz, 3'-H), 7.16 (d, 1H, J = 2.4 Hz, 6-H), 7.26 (dt, 1H, $J_{H-H}$ = 0.9, $J_{H-H}$ = 7.6 Hz, 5'-H), 7.34 (d, 1H, J = 8.7 Hz, 9-H), 7.47 (dt, 1H, $J_{H-H}$ = 1.8, $J_{H-H}$ = 8.4, $J_{H-F}^2$ = 5.7 Hz, 4'-H), 7.48 (dd, 1H, J = 2.5, 8.8 Hz, 8-H), 7.66 (dd, 1H, $J_{H-H}$ = 1.8, $J_{H-H}$ = 7.6, $J_{H-F}^2$ = 7.3 Hz, 6'-H); ms: m/z 316 $(M)^+$, 318 $[M+2]^+$.

*Anal.* Calcd. for: $C_{17}H_{14}ClFN_2O$: C, 64.45; H, 4.45; N, 8.85. Found: C, 64.52; H, 4.50; N, 8.94.

7-Chloro-5-(*p*-fluorophenyl)-3*H*-[1,4]benzodiazepin-2-one (**10**).

This compound was obtained as a yellow solid in 85% yield, mp 212°; ir (chloroform): ν N-H 3391, C=O 1693, C=N 1612, C-N 1350 and 1321, C-O 1288 and 1016 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 4.31 (bs, 2H, 3-H), 7.09 (AA'BB', 2H, $J_{H-H}$ = 8.7, $J_{H-F}^1$ = 9.6 Hz, 3-H, and 5-H phenyl protons of "C" ring), 7.17 (d, 1H, J = 8.7 Hz, 9-H), 7.29 (d, 1H, J = 2.4 Hz, 6-H), 7.46 (dd, 1H J = 2.4, 8.7 Hz, 8-H), 7.54 (AA'BB', 2H, $J_{H-H}$ = 9.0, $J_{H-F}^2$ = 5.4 Hz, 2-H and 6-H phenyl protons of "C" ring), 9.90 (bs, 1H, N-H) deuterium oxide exchangeable; ms: m/z 288 $(M)^+$, 290 $[M+2]^+$.

*Anal.* Calcd. for: $C_{15}H_{10}ClFN_2O$: C, 62.40; H, 3.49; N, 9.71. Found: C, 62.47; H, 3.41; N, 9.60.

7-Chloro-5-(*p*-fluorophenyl)-1-methyl-3*H*-[1,4]benzodiazepin-2-one (**11**).

This compound was obtained as a yellow solid in 36% yield, mp 214°; ir (chloroform): ν C=O 1678, C=N 1612, C-N 1340 and 1321, C-O 1269 and 1101 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.36 (s, 3H, N-$CH_3$), 3.76 (d, 1H, J = 10.8 Hz, 3-$H_a$), 4.67 (d, 1H, J = 10.8 Hz, 3-$H_b$), 7.17 (AA'BB', 2H, $J_{H-H}$ = 9.0, $J_{H-F}^1$ = 9.6 Hz, 3-H and 5-H, phenyl protons of "C" ring), 7.23 (d, 1H, J = 2.4 Hz, 6-H), 7.48 (d, 1H, J = 8.7 Hz, 9-H), 7.60 (dd, 1H, J = 2.7, 8.8 Hz, 8-H), 7.62 (AA'BB', 2H, $J_{H-H}$ = 9.0 and $J_{H-F}^2$ = 5.4 Hz, 2-H and 6-H, phenyl protons of "C" ring); ms: m/z 302 $(M)^+$, 304 $[M+2]^+$.

*Anal.* Calcd. for: $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 3.99; N, 9.26. Found: C, 63.57; H, 3.90; N, 9.18.

7-Chloro-1-ethyl-5-(*p*-fluorophenyl)-3*H*-[1,4]benzodiazepin-2-one (**12**).

This compound was obtained as a yellow semisolid in 45% yield; ir (chloroform): ν C=O 1676, C=N 1599, C-N 1350 and 1319, C-O 1157 and 1101 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.13 (t, 3H, J = 6.9 Hz, $CH_3$), 3.71 (q, 1H, J = 7.2 Hz, N-$CH_2$), 4.26 (q, 1H, J = 7.2 Hz, N-$CH_2$), 3.74 (d, 1H, J = 10.2 Hz, 3-$H_a$), 4.79 (d, 1H, J = 10.2 Hz, 3-$H_b$), 7.11 (AA'BB', 2H, $J_{H-H}$ = 9.0, $J_{H-F}^1$ = 9.3 Hz, 3-H and 5-H, phenyl protons of "C" ring), 7.26 (d, 1H, J = 2.4 Hz, 6-H), 7.37 (d, 1H, J = 9.0 Hz, 9-H), 7.52 (dd, 1H, J = 2.4, 8.7 Hz, 8-H), 7.60 (AA'BB', 2H, $J_{H-H}$ = 9.0 and $J_{H-F}^2$ = 5.4 Hz, 2-H and 6-H, phenyl protons of "C" ring); ms: m/z 316 $(M)^+$, 318 $[M+2]^+$.

*Anal.* Calcd. for: $C_{17}H_{14}ClFN_2O$: C, 64.45; H, 4.45; N, 8.85. Found: C, 64.53; H, 4.33; N, 8.73.

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