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One bond and long range  $^1\text{H}$ - $^1\text{H}$ ,  $^1\text{H}$ - $^{19}\text{F}$ ,  $^{13}\text{C}$ - $^1\text{H}$  and  $^{13}\text{C}$ - $^{19}\text{F}$  coupling constants for six 1,4-benzodiazepines are described. An unambiguous assignment of their carbon-13 resonances is carried out based on chemical shift theory and on the analysis of the fine splittings caused by one bond and long range couplings. Chemical shift and coupling constant values are reported for diazepam, chlordiazepoxide, oxazepam, nitrazepam, chlonazepam and flunitrazepam.

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The 1,4-benzodiazepines constitute an important group of psychotherapeutic drugs which have been extensively studied because of their sedative-hypnotic and tranquilizing properties (1,2). Recent work has been concerned with the relationship between molecular structures and biological activities (2,3,4). Crystal and molecular structures of several 1,4-benzodiazepines have been determined (4-9) and show that seven-membered rings retain a very similar boat conformation. However, there are few structural studies of this group of psychotherapeutic drugs in solution and they are generally restricted to proton magnetic resonance studies. In particular, the stereochemistry of the seven-membered lactam ring of the 1,4-benzodiazepines has been studied by  $^1\text{H}$  nmr and the inversion barrier of the seven-membered boat-form ring determined for some of these compounds (10-12). In the area of  $^{13}\text{C}$  nmr spectroscopy, the only study is a recent paper (13) that reports the chemical shifts and the  $T_1$  relaxation times of the carbon atoms of four compounds of the 1,4-benzodiazepine family. The study of proton and  $^{13}\text{C}$  nmr spectroscopy of these psychotherapeutic drugs is of theoretical as well as of biological importance and more work is needed in this area.

In this paper we report  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts, one bond and long range  $^1\text{H}$ - $^1\text{H}$ ,  $^1\text{H}$ - $^{19}\text{F}$ ,  $^1\text{H}$ - $^{13}\text{C}$  and  $^{13}\text{C}$ - $^{19}\text{F}$  coupling constants for the six 1,4-benzodiazepines illustrated in Figure 1. The six compounds include diazepam (I): 7-chloro-1-methyl-1,2-dihydro-5-phenyl-3H-1,4-benzodiazepin-2-one; chlordiazepoxide (II): 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepin-4-oxide; oxazepam (III): 7-chloro-3-hydroxy-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-4-one; nitrazepam (IV): 7-nitro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-4-one; clonazepam (V): 7-nitro-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-4-one; flunitrazepam (VI): 7-nitro-1-methyl-5-(2-fluorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-4-one. The various carbon resonances of these compounds have been assigned on the basis of chemical shift theory (14-16) and through a comparison of proton noise in decoupled and undecoupled spectra. The multiplicities of

the signals seen in the coupled spectra differentiate the methyl, methylene, methine and quaternary carbon resonances. An unambiguous assignment of carbon-13 resonances is carried out based on the analysis of the fine splittings caused by long range  $^{13}\text{C}$ - $^1\text{H}$  and  $^{13}\text{C}$ - $^{19}\text{F}$  couplings and single-frequency off-resonance proton decoupling experiments (16).

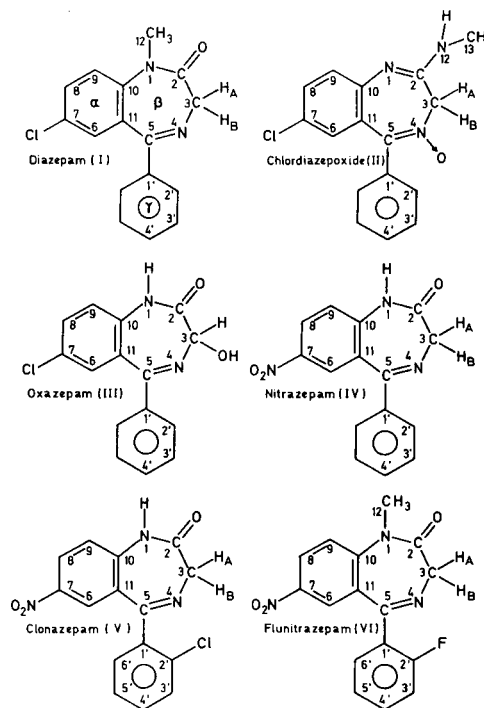


Figure 1: 1-4 benzodiazepines formulae.

#### EXPERIMENTAL

Proton nmr spectra for compounds I to III were obtained with a WH-90 Bruker spectrometer and those for compounds IV to VI were obtained with a Tm-250 Cameca spectrometer. Carbon-13 nmr spectra were obtained with a TSN-250 Cameca spectrometer operating at 62.86 MHz, both with and without proton noise decoupling. The specific conditions of measurement for the  $^{13}\text{C}$  spectra were as follows: spectral width, 15,000 Hz with 8192 memory points; acquisition time, 0.54 s; pulse width, 7.5  $\mu\text{s}$ ; number of pulses accumulated, decoupled spectra: 2000 to

Table I  
Proton Chemical Shifts ( $\delta$ ) for Compounds I to VI (a)

| Compound Atom | I         | II        | III       | IV        | V         | VI        |
|---------------|-----------|-----------|-----------|-----------|-----------|-----------|
| H-1           |           |           | 10.85     | 11.21     | 10.30     |           |
| H-3A          | 3.79      | 4.42 (b)  | 4.83      | 4.28 (c)  | 4.34 (d)  | 3.99      |
| H-3B          | 4.61      | 4.42 (b)  | 6.39      | 4.28 (c)  | 4.34 (d)  | 4.68      |
| H-6           | 7.22-7.80 | 6.79-7.55 | 7.23      | 8.04      | 7.78      | 7.93      |
| H-8           | 7.22-7.80 | 6.79-7.55 | 7.67      | 8.43      | 8.39      | 8.46      |
| H-9           | 7.22-7.80 | 6.79-7.55 | 7.32      | 7.50      | 7.48      | 7.83      |
| H-12          | 3.33      | 8.11      |           |           |           | 3.43      |
| H-13          |           | 2.85      |           |           |           |           |
| H-2'          | 7.22-7.80 | 6.79-7.55 | 7.22-7.78 | 7.45-7.58 |           |           |
| H-6'          | 7.22-7.80 | 6.79-7.55 | 7.22-7.78 | 7.45-7.58 | 7.48-7.71 | 7.17-7.78 |
| H-3'          | 7.22-7.80 | 6.79-7.55 | 7.22-7.78 | 7.45-7.58 | 7.48-7.71 | 7.17-7.78 |
| H-5'          | 7.22-7.80 | 6.79-7.55 | 7.22-7.78 | 7.45-7.58 | 7.48-7.71 | 7.17-7.78 |
| H-4'          | 7.22-7.80 | 6.79-7.55 | 7.22-7.78 | 7.45-7.58 | 7.48-7.71 | 7.17-7.78 |

(a) Perdeuteriodimethylsulfoxide was used as the solvent. (b) At 213°K in deuteriochloroform we find  $\delta(\text{H-3A}) = 4.09$  and  $\delta(\text{H-3B}) = 5.04$  ppm. (c) At 213°K in deuteriochloroform we find  $\delta(\text{H-3A}) = 3.95$  and  $\delta(\text{H-3B}) = 4.96$  ppm. (d) At 203°K in deuteriochloroform we find  $\delta(\text{H-3A}) = 3.95$  and  $\delta(\text{H-3B}) = 4.86$  ppm.

Table II  
Fine Splitting Pattern (appearance and assignment),  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{19}\text{F}$  Coupling Constants for Compounds I to VI (a)

| Compound Atom | I (b)               | II (b)             | III (b)                             | IV (b)                              | V (b)                               | VI (c)                               |
|---------------|---------------------|--------------------|-------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|
| H-1           |                     |                    | s                                   | s                                   | s                                   |                                      |
| H-3A          | d (H-3A, H-3B) 10.6 | s (broad) (e)      | d (H-3A, H-3B) 8.5                  | s (broad) (f)                       | s (broad) (g)                       | d (H-3A, H-3B) 11.6                  |
| H-3B          | d (H-3B, H-3A) 10.6 | s (broad) (e)      | d (H-3B, H-3A) 8.5                  | s (broad) (f)                       | s (broad) (g)                       | d (H-3B, H-3A) 11.6                  |
| H-6           | m (pr)              | m (pr)             | d (H-6, H-8) 2.4                    | d (H-6, H-8) 2.6                    | d (H-6, H-8) 2.6                    | dd (H-6, H-8) 2.6<br>(H-6, F-2') 0.8 |
| H-8           | m (pr)              | m (pr)             | dd (H-8, H-6) 2.4<br>(H-8, H-9) 8.8 | dd (H-8, H-6) 2.6<br>(H-8, H-9) 8.8 | dd (H-8, H-6) 2.6<br>(H-8, H-9) 9.1 | dd (H-8, H-6) 2.6<br>(H-8, H-9) 9.1  |
| H-9           | m (pr)              | m (pr)             | d (H-9, H-8) 8.8                    | d (H-9, H-8) 8.8                    | d (H-9, H-8) 9.1                    | d (H-9, H-8) 9.1                     |
| H-12          | s                   | q (H-12, H-13) 4.4 |                                     |                                     |                                     | s                                    |
| H-13          |                     | d (H-13, H-12) 4.7 |                                     |                                     |                                     |                                      |

(a) The Coupling Constant values are given in Hertz ( $\pm 0.2$  Hz). (b) Perdeuteriodimethylsulfoxide was used as a solvent. (c) Deuteriochloroform was used as a solvent. (e) At 213°K, in deuteriochloroform,  $J_{\text{H-3A, H-3B}} = J_{\text{H-3B, H-3A}} = 12.9$  Hz. (f) At 213°K, in deuteriochloroform,  $J_{\text{H-3A, H-3B}} = J_{\text{H-3B, H-3A}} = 10.9$  Hz. (g) At 203°K, in deuteriochloroform,  $J_{\text{H-3A, H-3B}} = J_{\text{H-3B, H-3A}} = 10.5$  Hz; s = singlet; d = doublet; dd = doublet of doublets; q = quadruplet; m = multiplet; m (pr) = multiplet (poor resolution).

3000, coupled spectra: 10,000 to 20,000. The gated decoupling technique was used for the coupled spectra. The chemical shift values ( $\delta$ ) are expressed in ppm relative to TMS and the coupling constants ( $^{\circ}J$ ) are expressed in Hertz (Hz).

The six compounds studied were kindly supplied by Hoffmann-LaRoche in high purity grade and after control analysis were used without further purification. The solutions were prepared by dissolving 0.5 g. of the sample in 1.5-2.5 ml. of perdeuteriodimethylsulfoxide. Since the study of the fine splitting patterns and the determination of the coupling constants values was not always possible with perdeuteriodimethylsulfoxide solutions, deuteriochloroform and perdeuterio-benzene were also used as solvents.

## Results and Discussion.

### Proton NMR Spectroscopy.

Proton nmr spectra were run for the six compounds in Figure 1 and the chemical shifts of the various proton

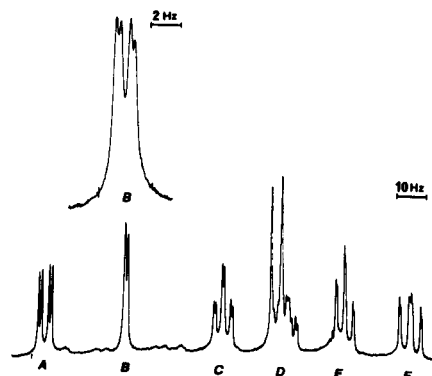


Figure 2: Flunitrazepam:  $^1\text{H}$  nmr expanded spectrum of the aromatic region (deuteriochloroform solution, 250 MHz).

Table III  
Carbon-13 Chemical Shifts ( $\delta$ ) for Compounds I to VI (a)

| Compound Atom | I      | II     | III    | IV     | V      | VI     |
|---------------|--------|--------|--------|--------|--------|--------|
| C-2           | 169.31 | 152.80 | 169.75 | 169.84 | 169.29 | 168.63 |
| C-3           | 56.76  | 64.53  | 82.81  | 57.07  | 57.02  | 56.73  |
| C-5           | 168.14 | 147.92 | 162.29 | 168.34 | 167.98 | 164.87 |
| C-6           | 129.00 | 128.81 | 129.22 | 126.50 | 124.87 | 123.94 |
| C-7           | 129.59 | 125.89 | 127.81 | 141.37 | 141.66 | 142.47 |
| C-8           | 131.54 | 129.08 | 131.72 | 126.28 | 126.35 | 126.15 |
| C-9           | 123.86 | 128.33 | 123.15 | 122.31 | 122.17 | 123.19 |
| C-10          | 142.72 | 140.54 | 137.96 | 145.04 | 144.26 | 147.42 |
| C-11          | 127.90 | 124.45 | 126.64 | 126.00 | 127.00 | 125.96 |
| C-12          | 34.27  |        |        |        |        | 34.62  |
| C-13          |        | 27.96  |        |        |        |        |
| C-1'          | 138.10 | 133.52 | 137.71 | 138.27 | 137.93 | 129.38 |
| C-2'          | 129.20 | 129.08 | 129.22 | 129.33 | 131.86 | 159.74 |
| C-6'          | 129.20 | 129.08 | 129.22 | 129.33 | 131.42 | 131.52 |
| C-3'          | 128.48 | 127.86 | 128.31 | 128.39 | 129.78 | 116.15 |
| C-5'          | 128.48 | 127.86 | 128.31 | 128.39 | 127.49 | 124.79 |
| C-4'          | 130.69 | 130.55 | 130.42 | 130.64 | 131.52 | 132.93 |

(a) Perdeuteriodimethylsulfoxide was used as a solvent.

Table IV  
Fine Splitting Pattern (appearance and assignment),  $^{13}\text{C}$ - $^1\text{H}$  and  $^{13}\text{C}$ - $^{19}\text{F}$  Coupling Constants for Compounds I to VI (a)

| Compound Atom | I (b)   | II (c)  | III (c)   | IV (c)  | V (c)                                     | VI (b)  |
|---------------|---|---|---|---|---|---|
| C-2           | m (pr)  | m (pr)  | m (pr)  | t (pr) (C-2, H-3) ~6  | t (C-2, H-3) 6.1                          | m (pr)  |
| C-3           | dd (C-3, H-3A) 130.9<br>(C-3, H-3B) 152.9                     | t (C-3, H-3A) 146.5<br>(C-3, H-3B) 146.5                      | d (C-3, H-3) 151.7  | t (C-3, H-3A) 142.1<br>(C-3, H-3B) 142.1                      | t (C-3, H-3A) 141.1<br>(C-3, H-3B) 141.1  | dd (C-3, H-3A) 134.1<br>(C-3, H-3B) 152.6                       |
| C-5           | m (pr)  | t (pr) (C-5, H-2') ~6<br>(C-5, H-6') ~6                       | m (pr)  | m (pr)  | m (pr)                                    | m (pr)  |
| C-6           | dd (C-6, H-6) 166.9<br>(C-6, H-8) 5.9                         | dd (C-6, H-6) 167.4<br>(C-6, H-8) 5.2                         | dd (C-6, H-6) 161.8<br>(C-6, H-8) 4.6                         | dd (C-6, H-6) 169.2<br>(C-6, H-8) 5.2                         | dd (C-6, H-6) 167.9<br>(C-6, H-8) 4.6     | dd (pr) (C-6, H-6) ~168<br>(C-6, H-8) ~5.5                      |
| C-7           | d (C-7, H-9) 6.5  | d (C-7, H-9) 5.2  | m (pr)  | m (pr)  | m (pr)                                    | m (pr)  |
| C-8           | dd (C-8, H-8) 167.7<br>(C-8, H-6) 6.1                         | dd (C-8, H-8) 162.2<br>(C-8, H-6) 5.2                         | dd (C-8, H-8) 161.8<br>(C-8, H-6) 4.6                         | dd (C-8, H-8) 170.9<br>(C-8, H-6) 5.2                         | dd (C-8, H-8) 170.9<br>(C-8, H-6) 6.1     | dd (C-8, H-8) 172.0<br>(C-8, H-6) 5.6                           |
| C-9           | d (C-9, H-9) 163.7  | d (C-9, H-9) 163.9  | d (C-9, H-9) 166.5  | d (C-9, H-9) 167.4  | d (C-9, H-9) 167.9                        | d (C-9, H-9) 164.6  |
| C-10          | t (pr) (C-10, H-6) ~8<br>(C-10, H-8) ~8                       | t (pr) (C-10, H-6) ~4.5<br>(C-10, H-8) ~4.5                   | t (pr) (C-10, H-6) ~7.5<br>(C-10, H-8) ~7.5                   | t (C-10, H-6) 7.9<br>(C-10, H-8) 7.9                          | t (C-10, H-6) 8.4<br>(C-10, H-8) 8.4      | t (pr) (C-10, H-6) ~7.5<br>(C-10, H-8) ~7.5                     |
| C-11          | m (pr)  | dd (C-11, H-6) 3.5<br>(C-11, H-9) 12.2                        | m (pr)  | d (C-11, H-9) 5.1   | d (C-11, H-9) 6.1                         | m (pr)  |
| C-12          | q (C-12, H-12) 140.2  |   |   |   |   | q (C-12, H-12) 140.6  |
| C-13          |   | q (C-13, H-13) 137.8  |   |   |   |   |
| C-1'          | t (C-1', H-3') 8.0<br>(C-1', H-5') 8.0                        | t (C-1', H-3') 7.3<br>(C-1', H-5') 7.3                        | t (C-1', H-3') 8.3<br>(C-1', H-5') 8.3                        | t (C-1', H-3') 5.2<br>(C-1', H-5') 5.2                        | t (C-1', H-3') 6.1<br>(C-1', H-5') 6.1    | m (pr)  |
| C-2'          | dt (C-2', H-2') 161.3<br>(C-2', H-4') 6.4<br>(C-2', H-6') 6.4 | dd (C-2', H-2') 163.9<br>(C-2', H-4') 5.2                     | dd (C-2', H-2') 161.8<br>(C-2', H-4') 4.6                     | dt (C-2', H-2') 162.2<br>(C-2', H-4') 7.0<br>(C-2', H-6') 7.0 | t (C-2', H-4') 7.6<br>(C-2', H-6') 7.6    | dt (C-2', F-2') 250.8<br>(C-2', H-4') 12.0<br>(C-2', H-6') 12.0 |
| C-6'          | dt (C-6', H-6') 161.3<br>(C-6', H-2') 6.4<br>(C-6', H-4') 6.4 | dd (C-6', H-6') 163.9<br>(C-6', H-4') 5.2                     | dd (C-6', H-6') 161.8<br>(C-6', H-4') 4.6                     | dt (C-6', H-6') 162.2<br>(C-6', H-2') 7.0<br>(C-6', H-4') 7.0 | dd (C-6', H-6') 170.9<br>(C-6', H-4') 7.6 | dd (C-6', H-6') 162.8<br>(C-6', H-4') 9.3                       |
| C-3'          | dd (C-3', H-3') 161.3<br>(C-3', H-5') 7.7                     | dd (C-3', H-3') 161.3<br>(C-3', H-5') 6.1                     | dd (C-3', H-3') 160.9<br>(C-3', H-5') 5.6                     | dd (C-3', H-3') 162.2<br>(C-3', H-5') 7.0                     | dd (C-3', H-3') 163.3<br>(C-3', H-5') 3.1 | fd (C-3', H-3') 163.7<br>(C-3', F-2') 22.2<br>(C-3', H-5') 7.4  |
| C-5'          | dd (C-5', H-5') 161.3<br>(C-5', H-3') 7.7                     | dd (C-5', H-5') 161.3<br>(C-5', H-3') 6.1                     | dd (C-5', H-5') 160.9<br>(C-5', H-3') 5.6                     | dd (C-5', H-5') 162.2<br>(C-5', H-3') 7.0                     | dd (C-5', H-5') 164.8<br>(C-5', H-3') 6.2 | fd (C-5', H-5') 166.5<br>(C-5', H-3') 6.5<br>(C-5', F-2') 3.1   |
| C-4'          | dt (C-4', H-4') 161.3<br>(C-4', H-2') 7.7<br>(C-4', H-6') 7.7 | dt (C-4', H-4') 161.3<br>(C-4', H-2') 6.1<br>(C-4', H-6') 6.1 | dt (C-4', H-4') 162.8<br>(C-4', H-2') 6.5<br>(C-4', H-6') 6.5 | dt (C-4', H-4') 162.2<br>(C-4', H-2') 7.0<br>(C-4', H-6') 7.0 | dd (C-4', H-4') 164.8<br>(C-4', H-6') 7.6 | dt (C-4', H-4') 162.8<br>(C-4', H-6') 8.3<br>(C-4', F-2') 8.3   |

(a) The Coupling Constant values are given in Hertz ( $\pm 0.7$  Hz). (b) Deuteriochloroform was used as a solvent. (c) Perdeuteriodimethylsulfoxide was used as a solvent; d = a doublet; dd = a doublet of doublets; t = a triplet; dt = a doublet of triplets; q = a quadruplet; fd = four doublets; m (pr) = multiplet (poor resolution).

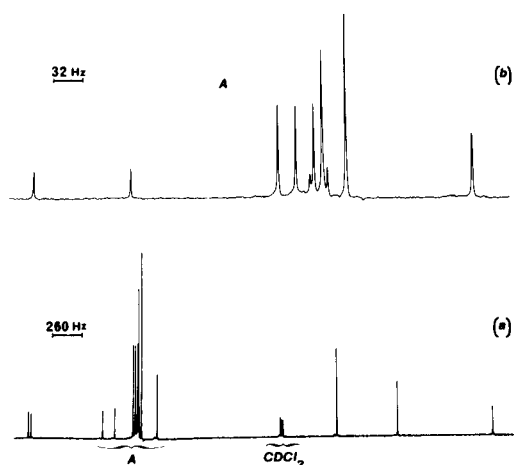


Figure 3: Proton decoupled  $^{13}\text{C}$  nmr spectrum of diazepam (deuteriochloroform solution, 62.86 MHz); (a): total spectrum; (b): part A expanded.

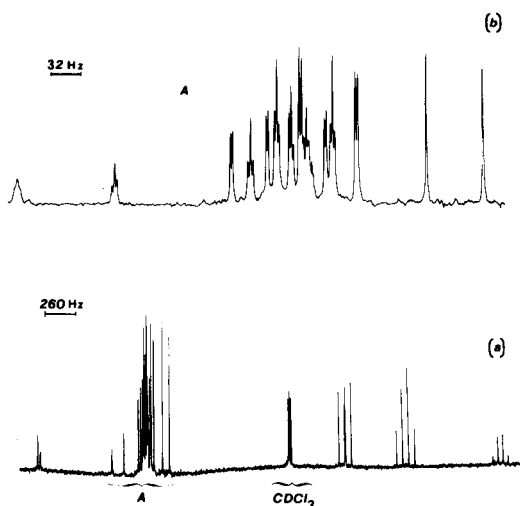


Figure 4: Undecoupled  $^{13}\text{C}$  nmr spectrum of diazepam (deuteriochloroform solution, 62.86 MHz); (a): total spectrum; (b): part A expanded.

resonances are listed in Table I. The coupling constants values  $^2J_{\text{H-H}}$  and  $^2J_{\text{H-F}}$  for the protons of the  $\alpha$  and  $\beta$  rings are listed in Table II. A full analysis of the proton nmr spectrum could be carried out only for compound VI, as the proton resonances of the  $\gamma$  phenyl ring for compounds I-V and the  $^1\text{H}$  resonances of the chlorinated ring ( $\alpha$ ) for compounds I and II could not be assigned.

The proton resonances for the phenyl rings ( $\alpha$  and  $\gamma$ ) of flunitrazepam (VI) in deuteriochloroform are shown in Figure 2. The proton resonances of the seven-membered ring are not shown but appear as follows: the H-12 resonance is a singlet ( $\delta$  3.50), and the H-3A ( $\delta$  3.83) and the H-3B ( $\delta$  4.94) resonances are doublets ( $J_{\text{H-3A,H-3B}} = 11.6$  Hz). The  $\alpha$  and  $\gamma$  phenyl ring part of the flunitrazepam spectrum shown in Figure 2 consists of six multiplets

marked with the letters A through F. Multiplets A, B and the high-field doublet in multiplet D arise from the  $\alpha$  phenyl ring and were unequivocally assigned. Multiplet A is a doublet of doublets assignable to H-8, which is interacting with protons H-9 and H-6. The doublet of doublets labeled B is the resonance for H-6 split by interactions with H-8 and F-2', whereas the high-field doublet in the multiplet D is due to H-9 which is interacting only with H-8. The multiplets C, D, E and F arise from the  $\alpha$  phenyl ring and were also unequivocally assigned as follows: the doublet of triplets labeled C is due to H-6' which is interacting with H-4', H-5' and F-2'; the multiplet D, which consists of fourteen resonance frequencies is the resonance for H-4' split by interactions with H-3', H-4', H-6', and F-2'; the six resonances of multiplet E are due to H-5' which is interacting with H-3', H-4' and H-6'; the eight resonances of multiplet F are due to H-3' which is interacting with H-4', H-5' and F-2'. These assignments were all corroborated by homonuclear single-frequency decoupling experiments.

The analysis of the proton nmr spectra for the other five compounds (I to V) were carried out in a similar way, but a complete assignment of the spectra (see Tables I and II) was not possible. The  $^1\text{H}$  nmr data obtained were mainly used to corroborate the  $^{13}\text{C}$  nmr assignments. In addition they also led to some important structural indications. In compound VI the observation of "through space" H-6 to F-2' coupling is in good agreement with the short H-6 to H-2' distance measured in the solid state for several 1,4-benzodiazepines. In compounds II, IV and V the inversion barrier of the seven-membered boat from ring ( $\beta$ ) is exceeded at room temperature and the  $^1\text{H}$  variable-temperature experiments showed that the two conformations of the  $\beta$  seven-membered ring are stabilized at temperatures as low as 213°K (compounds II and IV) and 203°K (compound V).

#### Carbon-13 NMR Spectroscopy.

The chemical shifts of the various carbon resonances for the six compounds are listed in Table III and the coupling constants values  $^1J_{\text{C-H}}$   $^1J_{\text{C-F}}$  are listed in Table IV.

The coupled and decoupled spectra of a deuteriochloroform solution of diazepam are reproduced in Figures 3 and 4. As evident from the decoupled spectrum shown in Figure 3, there are fourteen separate signals in the  $^{13}\text{C}$  nmr spectrum of I. These fourteen signals account for the resonances of all sixteen carbon atoms of I. Tracing (a) in Figure 4 shows the coupled spectrum. Starting at high field it is possible to assign the various features. The quartet at  $\delta$  34.80 is unequivocally assigned to C-12 ( $^1J_{\text{C-H}} = 140.2$ ) whereas the doublet of doublets at  $\delta$  56.91 is identified as the C-3 resonance split by interactions with H-3A and H-3B. The doublet at  $\delta$  122.60 is necessarily assigned to C-9 which is the only phenyl-ring carbon

characterized by a  $^1J_{C-H}$  coupling and the absence of  $^3J_{C-H}$  coupling. The complex resonance which is identified as region A is expanded in tracing (b) of Figure 4 and exhibits three doublets of doublets, two doublets of triplets, a doublet and a poorly resolved multiplet. The three doublets of doublets are respectively assigned to atoms C-3' and C-5' at  $\delta$  128.36 by  $^1J_{C-H}$ ,  $^3J_{C-3',H-5'}$  and  $^3J_{C-5',H-3'}$  atom C-6 at  $\delta$  129.83 by  $^1J_{C-H}$  and  $^3J_{C-6,H-8'}$  and atom C-8 at  $\delta$  131.46 by  $^1J_{C-H}$  and  $^3J_{C-8,H-6}$ . Several criteria allow one to distinguish between the resonances of these three different carbon atoms: the C-3'/C-5' signal is twice as intense as those for atoms C-6 or C-8; the C-8 and C-6 resonances are slightly shifted to lower fields compared to the C-3'/C-5' atoms by the presence of the chlorine substituent; the resonance for C-6 should be at higher field than that for C-8 because of the presence of the C-11 atom (13,17).

The two doublets of triplets in region A of the diazepam spectrum (Figure 4) are assigned to C-4' at  $\delta$  130.64 by  $^1J_{C-H}$ ,  $^3J_{C-4',H-2'}$  and  $^3J_{C-4',H-6'}$  and C-2'/C-6' at  $\delta$  129.45 by  $^1J_{C-H}$ ,  $^3J_{C-2',H-4'}$ ,  $^3J_{C-2',H-6'}$ ,  $^3J_{C-6',H-2'}$  and  $^3J_{C-6',H-4'}$ . The doublet at  $\delta$  129.98 arises from a quaternary carbon atom and is unambiguously assigned to atom C-7 by  $^3J_{C-7,H-9}$ . Finally, the poorly resolved multiplet at  $\delta$  129.20 also comes from a quaternary carbon atom and can be assigned to atom C-11 by comparison with the literature data (18,19).

The resonances for atoms C-1', C-10, C-2, and C-5 of diazepam (I) are found to low field of the complex region A. There is a triplet at  $\delta$  138.16 which is due to a quaternary carbon atom and can be assigned to C-1' by  $^3J_{C-1',H-3'}$  and  $^3J_{C-1',H-5'}$  by comparison with the data obtained for benzophenonemethylimine (13). The poorly resolved triplet at  $\delta$  142.58 is assigned to C-10 by comparison with literature data and  $^3J_{C-10,H-8}$  and  $^3J_{C-10,H-6}$  (17). Two unresolved quaternary carbon resonances are seen at lowest field and are assigned as  $\delta$  169.79 for C-2 and  $\delta = 168.85$  for C-5 as per the literature (13-16). These assignments, particularly the C-1' and C-2'/C-6' assignments, are consistent with the results of the nmr study of I in the presence of  $Cu^{2+}$  ions (20).

The analysis of the  $^{13}C$  nmr spectra for the other five compounds II to VI was carried out in a similar way, the assignments being corroborated by proton single frequency off-resonance decoupling experiments as often as the corresponding proton resonance frequencies could be well-defined. Chemical shift data are given in Table III and coupling constants are summarized in Table IV.

Generally speaking the six compounds can be divided up into two groups: the chlorinated 1,4-benzodiazepines (I to III) and the nitrated 1,4-benzodiazepines (IV to VI). The groups are distinguished by significant differences in the  $^{13}C$  parameters of the  $\alpha$  phenyl ring. The C-2 chemical shifts are very similar for compounds I and III to VI; for

compound II this value is shifted upfield (16 ppm) due to the fact that there are two nitrogen atoms in the C-2 direct environment. The fine splitting pattern is only resolved for compounds IV and V ( $^2J_{C-2,H-3} \cong 6$  Hz) and the  $^2J$  values are consistent with the observations of Takeuchi *et al.* (21).

Among the six compounds studied, II and III are characterized by differences in the environment of atoms C-3 and C-5. The presence of the N-4 $\rightarrow$ O bonding (II) causes a downfield shift of 7.5 ppm for atom C-3 and an upfield shift of 20 ppm for C-5 due to the anisotropy of the N-4 electronic doublets. The 3-hydroxyfunction of compound III leads to downfield shift of 24 ppm for C-3 and an upfield shift of 6 ppm for C-5. Moreover, for the compound VI, the fluorine substituent induces a slightly upfield shift ( $\sim 3$  ppm) at C-5. Concerning the coupling constants in III, C-3 is directly bonded to only one proton and consequently the splitting pattern is a doublet; in compounds II, IV and V, at the observation temperature (300°K),  $J_{C-3,H-3A} = J_{C-3,H-3B}$  and the splitting pattern is a triplet; in compounds I and VI H-3A and H-3B are inequivalent at the observation temperature and a doublet of doublets is observed displaying the higher conformational stability of these two compounds. These various results are consistent with the  $^1H$  nmr observations previously described. The fine splitting pattern observed for atom C-5 is only resolved for compound II.

The three carbon atoms C-6, C-7 and C-8 are under the prevailing influence of the 7-substituent and their  $^{13}C$  chemical shifts allow a clear differentiation between the chlorinated 1,4-benzodiazepines from the nitrated ones. Various secondary effects account for minor  $\delta C_i$  variations inside each group: particularly, in the case of C-6 the upfield shift (1.5 and 2.5 ppm respectively) observed for V and VI may be explained by the proximity of chlorine (V) and fluorine (VI) substituents. These results are consistent with the observation of a "through space" coupling between H-6 and F-2' for VI (*cf.*  $^1H$  nmr).

The C-9 chemical shift values are homogeneous except for II which is characterized by a downfield shift of 5 ppm probably due to the anisotropy of the N-1 electronic doublets (note that II is the only compound characterized by the absence of N-1 substituent).

Atoms C-10 and C-11 belong to  $\alpha$  and  $\beta$  rings and their  $^{13}C$   $\delta$ -values depend on several related effects, particularly the C-7, N-1, C-2, C-3, and N-4 substituents. However, at the C-10 level the nitrated 1,4-benzodiazepines (IV to VI) are still differentiated from the chlorinated ones (I to III) while, on the other hand the  $\delta$  values for C-11 show little variation among the six compounds.

The compounds II, V and VI are characterized by differences in the C-1' environment. The presence of the N-4 $\rightarrow$ O bonding (II) causes an upfield shift of 4.5 ppm for C-1' due to the anisotropy of the N-4 electronic doublets. As expected the fluorine substituent causes a pronounced

upfield shift ( $\sim 9$  ppm) while the chlorine substituent does not shift the C-1' resonance frequency.

With regard to the other five carbon atoms of the  $\gamma$  phenyl ring (C-2', C-6', C-3', C-5' and C-4') it is possible to distinguish two groups of compounds: the compounds I to IV, which are not substituted at C-2' are characterized by a single  $^{13}\text{C}$  resonance frequency corresponding to C-2' and C-6' and another  $^{13}\text{C}$  resonance frequency corresponding to C-3' and C-5'; moreover  $^{13}\text{C}$  variable temperature experiments display the chemical shift equivalence of C-2'/C-6' and C-3'/C-5' even at temperatures as low as 213°K. The C-2'/C-6', C-3'/C-5', and C-4' resonance frequencies of these four compounds are precisely the same and consistent with the literature values (14-16). However, the C-2'/C-6' splitting patterns display the magnetic inequivalence of H-2' and H-6' in compounds I and IV (doublet of triplets) while the C-3'/C-5' fine splitting patterns display the magnetic inequivalence of H-3' and H-5' in the four compounds (doublet of doublets). Concerning the compounds V and VI, the  $\delta^{13}\text{C}$ ,  $n\text{J}_{\text{CH}}$  and  $n\text{J}_{\text{CF}}$  are perfectly consistent with chlorobenzene and fluorobenzene literature data (15,16).

The compounds I, II and V have recently been studied by Singh, *et al.* (13). Their  $^{13}\text{C}$  chemical shift assignments are quite different from ours, particularly with regard to diazepam (I) and chlordiazepoxide (II). In their assignments these authors have not accounted for the fine splittings caused by long range  $^{13}\text{C}$ - $^1\text{H}$  couplings.

In summary, in spite of a "through space" coupling of H-6 and F-2' in compound VI and of the short H-6 to H-2' distance measured in the solid state, the C-2', C-6', C-3', and C-5' resonance frequencies display the chemical shift equivalence of C-2' and C-6' as well as C-3' and C-5', showing thus that there is a sufficiently rapid rotation of the  $\gamma$  phenyl ring about the C-5 to C-1' axis.

At the observation temperature and for the compounds I and VI the  $^1\text{H}$  and  $^{13}\text{C}$  nmr data show a slow exchange (on the nmr time scale) between the two boat forms of the  $\beta$  ring, while, for the compounds II, IV and V, at room temperature, the inversion barrier of the seven-membered

ring ( $\beta$ ) is exceeded; temperatures as low as 203 to 213°K are necessary to stabilize the two conformations of the  $\beta$  seven-membered ring for these three compounds.

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