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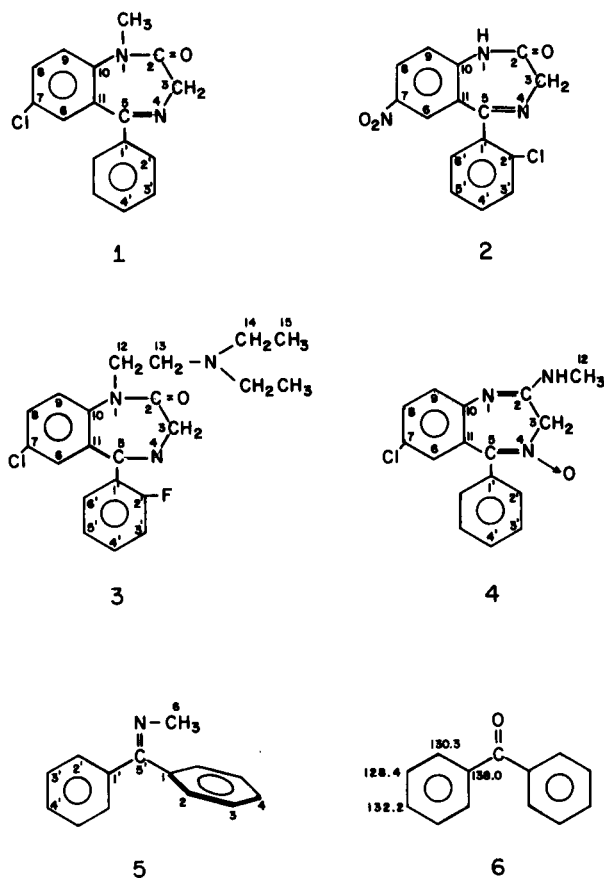
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The natural abundance carbon-13 nuclear magnetic resonance spectra of diazepam, clonazepam, flurazepam and chlordiazepoxide were recorded in suitable solvent using the Fourier transform technique on a JEOL FX-60 spectrometer. The relaxation time (T_1) of these compounds were also measured. The chemical shift of the various carbon resonances have been assigned on the basis of chemical shift theory, multiplicity generated in single-frequency off-resonance decoupled spectra, relaxation time and the chemical shifts of the model compounds.

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The drugs of benzodiazepine group constitute an important class of sedative-hypnotics. The study of natural abundance ^{13}C nmr spectroscopy of these drugs are of theoretical as well as of biological importance. In our previous studies, we have reported the assignments of ^{13}C nmr spectra of various classes of synthetic and natural therapeutic agents (1-9). In the present investigation, we wish to report the complete assignments of the carbon resonances in the ^{13}C nmr spectra of some benzodiazepines. These include diazepam **1** (7-chloro-1,3-dihydro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one), clonazepam **2** (7-nitro-5-(2-chlorophenyl)-1,3-trihydro-1,4-benzodiazepin-2-one), flurazepam **3** (7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-3H-1,4-benzodiazepin-2-one) and chlordiazepoxide **4** (7-chloro-5-phenyl-1,3-dihydro-3H-1,4-benzodiazepin-2-aminomethyl-4-oxide). The ^{13}C nmr spectrum of benzophenonemethylimine **5** was also determined as a model compound for comparative assignments of the various carbon resonances of **1**, **2** and **3**.

The natural abundance ^{13}C nmr spectra of **1**, **2**, **3**, **4** and **5** were recorded on a JEOL FX-60 spectrometer in a suitable solvent using tetramethylsilane as a reference and the deuterium resonance of the solvent as an internal lock. In all cases proton noise decoupled and single-frequency off-resonance decoupled (SFORD) spectra were taken. The relaxation time (T_1) of **1**, **2**, **3** and **4** were also measured which differentiated the quaternary carbons from other protonated carbons. The multiplicities generated in SFORD spectra differentiated the methyl, methylene, methine and quaternary carbon resonances. However, the SFORD spectra were unable to differentiate the resonances of some aromatic carbons. The assignments of ^{13}C nmr spectra of **1**, **2**, **3** and **4** are complicated due to very close chemical shifts of some carbon resonances. The various carbon resonances of **1**, **2**, **3**, **4** and **5** were assigned on the basis of chemical shift theory, multiplicities generated in SFORD spectra, intensity of signals, comparison with structurally related compounds and relaxation times.



Discussion.

Benzophenonemethylimine (5).

There are seven signals in the downfield and one signal in the upfield region in the ^{13}C nmr spectrum of **5** (Table I). The upfield signal at 41.3 ppm is assigned to the carbon of methyl group. The molecular model of **5** using Dreiding Stereomodels shows that the one phenyl ring in the benzophenonemethylimine molecule is coplanar to the imine group while the other is out-of-plane due to the methyl group steric interaction. Hence, the carbon resonances of C-1 and C-1' will be observed at different posi-

Table I

Carbon-13 Chemical Shifts of Benzophenonemethylimine

Assignment (a)	Multiplicity (b)	Chemical Shift (c)
C-5	s	169.2
C-1'	s	139.8
C-1	s	136.4
C-4, C-4'	d	129.7
C-2'	----	128.5
C-2, C-3'	d	128.1
C-3	----	127.7
C-6	q	41.3

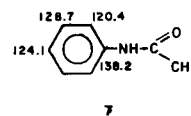
(a) Numbering of the carbons are shown in the structure. (b) Signal multiplicity obtained from SFORD, s = singlet, d = doublet, t = triplet and q = quartet. (c) Chemical shifts are expressed in ppm relative to tetramethylsilane.

tions and C-1 will be shifted upfield compared to C-1' due to methyl group steric hinderance. Thus the singlets at 169.2, 139.8 and 136.4 ppm are assigned to C-5, C-1' and C-1, respectively. The carbon resonances at 129.7, 128.1, 128.5 and 127.7 ppm have been attributed to C-4 and C-4' as one signal, C-2 and C-3' as one signal, C-2' and C-3, respectively, on the basis of chemical shift theory (10,11), signal intensity and comparison with the chemical shifts of benzophenone **6** (10).

Diazepam (1).

The chemical shifts of various carbon resonances of **1** and the relaxation times are recorded in Table II. The SFORD spectrum exhibited four singlets for the six quaternary carbons which were further supported by their longer relaxation times compared to the protonated carbons. On the basis of chemical shift theory (10,11) and comparing the chemical shifts of the corresponding quaternary carbons of **5** and acetanilide **7** (12), the singlets at 137.8, 142.0, 168.3 and 169.3 ppm are assigned to C-7 and C-11 as one signal, C-1' and C-10 as one signal, C-2 and C-5, respectively. The assignments of C-2 and C-5 may be interchanged. The phenyl ring attached at position 5 of the benzodiazepine nucleus can rotate along C-5 to C-1' axis. The C-4' carbon should have a shorter T_1 compared to C-2' and C-3' because C-2' and C-3' show more motion which results into longer T_1 values due to less favorable dipole-dipole interaction. Considering this fact and comparing the chemical shifts of the corresponding carbons of **5**, the doublets centered at 127.9 and 128.9 and signal at 129.3 ppm are assigned to C-3', C-2' and C-4', respectively. The spectrum of model compound **5** indicates that the imino group causes a significant downfield shift at ipso carbon of phenyl rings but a very small shift at ortho, meta and para carbons. So the chemical shifts of C-6, C-8

and C-9 will be mostly under the influence of the chloro and *N*-methyl acetanilido groups. The remaining three doublets centered at 122.2, 130.1 and 131.0 ppm are attributed to the carbon resonances of C-9, C-6 and C-8, respectively. These are comparable with their calculated values. The triplet centered at 56.5 ppm and quartet centered at 34.4 ppm are assigned to C-3 and C-12, respectively.



Clonazepam (2).

As is evident from Table III, there are thirteen separate signals in the downfield and one signal in the upfield region in the ^{13}C nmr spectrum of **2**. These fourteen signals account for the resonances of all the fifteen carbons of **2**. The SFORD spectrum of **2** showed seven separate singlets which were also confirmed by their longer relaxation times. The two farthest downfield singlets at 169.3 and 167.9 ppm are assigned to C-5 and C-2, respectively, and these, however, can be interchanged. These assignments are further supported with the corresponding carbon chemical shifts of **1**, **5** and **7** (12). The other five singlets at 144.4, 141.7, 138.0, 131.9 and 127.0 ppm are assigned to the carbon resonances of C-7, C-10, C-1', C-2' and C-11, respectively. These assignments are in agreement with their calculated values obtained by considering the substituent effects of the nitro, the acetanilido and the chloro groups (10,11) on the chemical shifts of **5**. The chemical shifts of C-6, C-8 and C-9 resonances are under the influence of the nitro and the acetanilido groups only because the imino group causes small shifts. On this basis, the doublets centered at 122.2, 124.9 and 126.4 ppm have been assigned to C-9, C-6 and C-8, respectively. The signals at 131.4, 129.8 and 127.5 ppm are assigned to C-4' and C-6' as one signal, C-3' and C-5', respectively, on the basis of signal intensity and considering the substituent effect of chlorine on the phenyl ring of **5**. The triplet centered at 57.1 ppm is attributed to C-3 and comparable with the chemical shift of the corresponding carbon of **1**.

Flurazepam (3).

The chemical shifts of the various carbon resonances of **3** obtained from its ^{13}C nmr spectrum and their relaxation times are recorded in Table IV. There are thirteen separate signals in the downfield and five separate signals in the upfield region which account for the resonances of all the twenty-one carbons of **3**. Fluorine causes 34.8 ppm downfield shift and 12.9 ppm upfield shift (10,11) to its ipso and ortho carbons in benzene nucleus. Thus, the singlets at 165.8 and 126.4 ppm are best assigned to C-2' and C-1', respectively, by considering the fluorine

Table II
Carbon-13 Chemical Shifts of Diazepam

Assignment (a)	Multiplicity (b)	Relaxation Time (d)	Chemical Shift (c)
*C-5	s	16.40	169.3
*C-2	s	17.80	168.3
C-1', C-10	s	18.70	142.0
C-7, C-11	s	16.00	137.8
C-8	d	0.87	131.0
C-6	d	0.91	130.1
C-4'	----	0.83	129.3
C-2'	d	0.93	128.9
C-3'	d	1.20	127.9
C-9	d	0.89	122.2
C-3	t	0.41	56.5
C-12	q	2.30	34.4

(a,b, and c) See footnote in Table I. (d) Relaxation time was measured in undegassed solution.

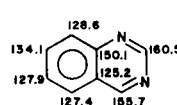
substituent effect on the phenyl ring of **5**. The singlet at 168.1 ppm is attributed to both C-2 and C-5, based on the signal intensity and comparing the chemical shifts of **1**, **2**, **5** and **7** (12). The resonance of C-7 is represented at 140.6 ppm by comparing the chemical shift of **1**. The C-10 and C-11 are crowded due to the bulky *N,N*-diethylaminoethyl side chain. Hence these carbons will be shielded and consequently appear at upfield. Therefore, the singlets at 127.2 and 129.9 ppm are assigned to C-10 and C-11, respectively, which may be interchanged. On the basis of the chemical shift theory (10,11) and comparison with the corresponding carbon chemical shifts of **1**, the signals at 132.3, 131.5 and 117.0 ppm have been assigned to C-8, C-6 and C-9, respectively. Furthermore, the signals at 132.7, 128.3, 124.4 and 115.5 ppm are assigned to C-4', C-6', C-5' and C-3', respectively. The above assignments are based on the fluorine substituent effect on benzene nucleus of **5**, where the assignments of C-4' and C-8 may be interchanged.

The triplet centered at 57.2 ppm is assigned very easily to C-3 by comparing the assignment of **1**. The resonances of the carbon of both methyl groups are represented at 11.7 ppm, on the basis of chemical shift theory, relaxation time, signal intensity and the multiplicity observed in SFORD spectrum. The remaining three triplets are due to the carbon resonances of C-12, C-13 and C-14. The triplet centered at 47.3 ppm is assigned to C-14, based on the signal intensity. Furthermore, the triplets centered at 46.3 and 50.4 ppm are represented to C-12 and C-13, respectively, and these, however, can be interchanged.

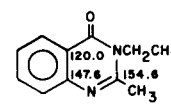
Chlordiazepoxide (**4**).

The chemical shifts and relaxation times of the carbon

resonances of chlordiazepoxide, recorded in Table V, exhibit six quaternary singlets, three doublets and two unresolved signals in the downfield region in the ^{13}C nmr spectrum of **4**. The isolation of the quaternary carbons from protonated carbons was also supported by their longer relaxation times. The quartet centered at 27.9 ppm and triplet at 64.4 ppm in the upfield region are assigned to C-12 and C-3, respectively. The singlets at 152.7, 147.8, 140.4 and 125.7 ppm are assigned to the carbon resonances of C-2, C-5, C-10 and C-11, respectively, on the basis of the comparison of the chemical shifts of **8** (10) and **9** (4). The chloro group attached to a benzene nucleus causes a 6.2 ppm downfield shift for the ipso carbon (10). The singlets at 133.2 and 124.1 ppm are assigned to C-7 and C-1', respectively. The assignments of C-1' and C-11 could be interchanged. The phenyl ring attached at position 5 of the benzodiazepine group can rotate along C-5 to C-1' axis. The C-2' and C-3' will take longer times to relax as compared to C-4', due to more angular motion. So the relaxation times observed for C-2' and C-3' will be longer than C-4'. On the basis of this phenomenon and signal intensity, the signals at 128.9, 127.8 and 128.7 ppm are attributed to the carbon resonances of C-2', C-3' and C-4', respectively. These assignments are further supported by the corresponding carbon chemical shifts of **1**. By comparing the chemical shifts of **8** and **9** and considering the substituent effects of chlorine on benzene nucleus (10,11), the resonances of C-8 and



8



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Table III
Carbon-13 Chemical Shifts of Clonazepam

Assignment (a)	Multiplicity (b)	Relaxation Time (d)	Chemical Shift (c)
*C-5	s	2.20	169.3
*C-2	s	5.70	167.9
C-7	s	2.30	144.4
C-10	s	3.50	141.7
C-1'	s	5.70	138.0
C-2'	s	9.10	131.9
C-4', C-6'	----	0.25	131.4
C-3'	----	0.16	129.8
C-5'	d	0.19	127.5
C-11	s	3.60	127.0
C-8	d	0.15	126.4
C-6	d	0.17	124.9
C-9	d	0.17	122.2
C-3	t	0.09	57.1

(a,b,c and d) See footnote in Table I and Table II.

Table IV
Carbon-13 Chemical Shifts of Flurazepam

Assignment (a)	Multiplicity (b)	Relaxation Time (d)	Chemical Shift (c)
C-2, C-5	s	7.60	168.1
C-2'	s	13.70	165.8
C-7	s	10.20	140.6
*C-4'	----	0.51	132.7
*C-8	----	0.88	132.3
C-6	----	0.53	131.5
**C-11	s	8.50	129.9
C-6'	d	0.38	128.3
**C-10	s	13.20	127.2
C-1'	s	16.10	126.4
C-5'	d	0.42	124.4
C-9	d	0.56	117.0
C-3'	d	0.90	115.5
C-3	t	0.29	57.2
***C-13	t	0.38	50.4
C-14	t	0.71	47.3
***C-12	t	0.35	46.3
C-15	q	2.00	11.7

(a,b,c and d) See footnote in Table I and Table II.

C-9 both occur at 130.4 ppm and the resonance of C-6 at 128.2 ppm. The assignments of C-4' and C-6 may be interchanged.

EXPERIMENTAL

Both the proton-noise decoupled and single-frequency off-resonance decoupled spectra of **1**, **2**, **3**, **4** and **5** were recorded on

a JEOL FX-60 spectrometer equipped with a Fourier transform system. The samples were run in 10 mm tube, using deuteriochloroform as solvent and internal lock in case of **1**, **3**, and **5** and DMSO-d₆ as solvent and internal lock in case of **2** and **4**. In all cases, tetramethylsilane was used as a reference. The spectrometer setting during experiment was as follows: spectral width 4K Hz, pulse width 12μ sec (60°) and data points 4K. The relaxation time measurements of **1**, **2**, **3**, and **4** were carried out in undegassed solution and were automatically calculated by the

Table V

Carbon-13 Chemical Shifts of Chlordiazepoxide

Assignment (a)	Multiplicity (b)	Relaxation Time (d)	Chemical Shift (c)
C-2	s	5.10	152.7
C-5	s	7.70	147.8
C-10	s	7.00	140.4
C-7	s	6.00	133.2
C-8, C-9	d	0.34	130.4
C-2'	d	0.35	128.9
*C-4'	----	0.20	128.7
*C-6	----	0.20	128.2
C-3'	d	0.35	127.8
**C-11	s	4.57	125.7
**C-1'	s	4.90	124.1
C-2	t	0.20	64.4
C-12	q	0.93	27.9

(a,b,c and d) See footnote in Table I and Table II.

FX-60 computer by least squares analysis (13) of the plot of I_n ($I_\infty - I_T$) vs T.

Benzophenonemethylimine was prepared in our laboratory by following the method reported earlier (14); b.p. 169° (17 mm/Hg), nmr δ (CCl_4), 3.1 (s, 3H, NCH_3) and 7.0-7.8 (m, 10H, aromatic).

Acknowledgment.

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