A ^{13}C-NMR Assignment Study of a Series of 2,3,4,5-Tetrahydro-1-methyl-1*H*-1,5-benzodiazepine-2,4-diones

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The natural abundance ^{13}C-nmr spectra of a series of 2,3,4,5-tetrahydro-1-methyl-1*H*-1,5-benzodiazepine-2,4-diones have been recorded: two of these compounds, clobazam and triflubazam, are clinically used as psychotherapeutic agents. The assignments of the various resonances have been made by chemical shift arguments, by the analysis of the fine splittings caused by one bond and long range couplings, and also by comparison with model compounds.

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Benzodiazepines are drugs with particular clinical interest, well known for their tranquilizing and sedative-hypnotic properties [1]; their muscle relaxant and anticonvulsant effects are also of considerable importance. A number of investigations concerned with the stereochemistry in solution of several 1,4- and 1,5-benzodiazepine derivatives have been accomplished by us [2a-e,3] in the aim at contributing a better understanding of the relationship between molecular structure and biological activity in the field of psychotherapeutic agents.

Since the aforementioned stereochemical and conformational assignments have been made on the basis of ^{1}H-nmr only, it appeared very convenient for future studies to broaden the scope of the available techniques, thus ^{13}C-nmr spectroscopy is a logical and powerful tool to be explored in this connection. In particular, ^{13}C-nmr data derived from a representative series of 2,3,4,5-tetrahydro-1-methyl-1*H*-1,5-benzodiazepine-2,4-diones (Figure 1), which have not previously been studied by this technique, may very well provide additional information to be used in SAR studies [4] concerning neuroleptics, together with already available ^{13}C-nmr parameters of some 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones [5-10], 3*H*-1,4-benzodiazepine 4-oxides [5,7,9], 2,3-dihydro-1*H*-1,4-benzodiazepines [8,11], 2,3-dihydro-1*H*-1,5-benzodiazepin-2-ones [12] and thieno[2,3-*b*][1,5]benzodiazepines [13].

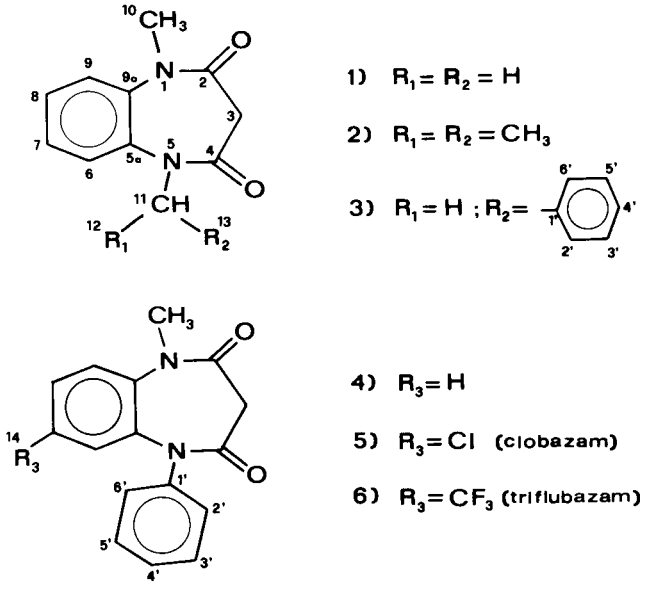

Figure 1. 2,3,4,5-Tetrahydro-1-methyl-1*H*-1,5-benzodiazepine-2,4-diones under investigation.

Results and Discussion.

The chemical shifts of the various carbon resonances for six 2,3,4,5-tetrahydro-1-methyl-1*H*-1,5-benzodiazepine-2,4-diones (**1** to **6**) are listed in Table 1 and the coupling constant values J_{C-H} J_{C-F} for **1**, **4** to **6** are listed in Table

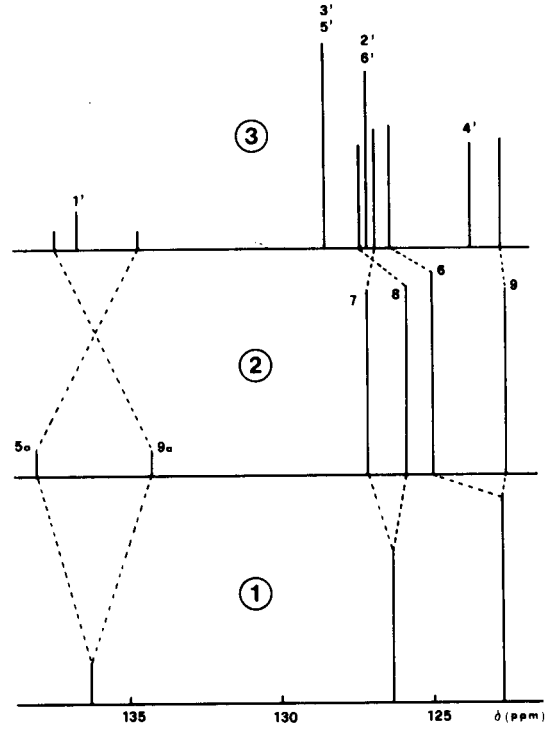

Figure 2. PND ^{13}C Aromatic Resonances for Compounds **1** to **3**.

Table 1

CMR Shifts for Compounds **1** to **6**

Compound Carbon	1	2	3	4	5	6
2	165.84	166.46	165.37	164.54	164.25	164.08
3	44.36	45.33	44.40	44.94	44.85	44.72
4	165.84	165.55	165.77	165.73	165.33	165.25
5a	136.28	138.06	134.83	136.09	137.02	136.14
6	122.76	124.98	126.43	126.73	126.94	123.40
7	126.41	127.10	126.93	126.26	131.59	128.06
8	126.41	125.88	127.40	126.26	125.97	123.40
9	122.76	122.66	122.81	122.62	123.87	123.40
9a	136.28	134.26	137.37	137.10	135.68	139.58
10	35.49	34.91	35.13	35.47	35.54	35.58
11	35.49	51.33	51.01			
12		20.28 [a]				
13		22.28 [a]				
1′			136.69	140.85	140.37	140.14
2′,6′			127.09	127.90	127.94	127.81
3′,5′			128.55	129.24	129.52	129.55
4′			123.73	127.48	127.94	127.81
14						126.52

[a] These values may be interchanged.

2. Figures 2 and 3 show the aromatic absorptions of **1** to **3** and **4** to **6** respectively. The ^{13}C resonances have been assigned on the basis of chemical shift theory [14a,15] and through a comparison of the proton-noise decoupled (PND) spectra to the proton coupled ones. The multiplicities of the signals differentiate the methyl, methylene, methine and quaternary carbon resonances.

The comparison of coupled and decoupled spectra of a deuteriochloroform solution of **1** permits the identification of six separate signals which account for the resonances of all eleven carbon atoms of **1**, owing to the symmetry of the molecule. Starting at high field it is possible to assign the various features: the quartet at δ 35.49 is unequivocally assigned to C-10 and C-11 ($^1J_{C\text{-}H}$ = 152.0) whereas the triplet at δ 44.36 is identified as the C-3 resonance ($^1J_{C\text{-}H}$ = 135.0). The doublets of doublets at δ 122.76 and 126.41 are assigned to C-6, C-9 and C-7, C-8 respectively: the resonance for C-6, C-9 should be at higher field than that for C-7, C-8 because of the presence of C-5a, C-9a quaternary atoms [5,7,11]. Finally two quaternary carbon resonances are seen at lowest field and are assigned as δ 136.28 for C-5a, C-9a and δ 165.84 for C-2, C-4.

Table 2

Fine Splitting Pattern (appearance and assignment), ^{13}C-^1H and ^{13}C-^{19}F Coupling Constants for Compounds **1**, **4** to **6** [a]

Compound Carbon	1	4	5	6
2	t (pr), (C-2, H-3), 5.0	t (pr), (C-2, H-3), 6.3	t (pr), (C-2, H-3), 7.8	t (pr), (C-2, H-3), 6.8
3	t, (C-3, H-3), 135.0	t, (C-3, H-3), 140.0	t, (C-3, H-3), 137.5	t, (C-3, H-3), 132.5
4	t (pr), (C-4, H-3), 5.0	t (pr), (C-4, H-3), 6.3	t (pr), (C-4, H-3), 7.8	t (pr), (C-4, H-3), 6.8
5a	t, (C-5a, H-7), 6.9 (C-5a, H-9), 6.9	t, (C-5a, H-7), 5.3 (C-5a, H-9), 5.3	d (pr), (C-5a, H-9), 5.3	d (pr), (C-5a, H-9), 7.2
6	dd, (C-6, H-6), 156.0 (C-6, H-8), 6.3	dd, (C-6, H-6), 162.7 (C-6, H-8), 7.5	dd, (C-6, H-6), 168.8 (C-6, H-8), 5.6	dd, (C-6, H-6), 161.3 (C-6, H-8), 5.6
7	dd, (C-7, H-7), 160.0 (C-7, H-9), 6.3	dd, (C-7, H-7), 160.0 (C-7, H-9), 7.5	d, (C-7, H-9), 9.3 [b]	d, (C-7, H-9), 5.6 [b]
8	dd, (C-8, H-8), 160.0 (C-8, H-6), 6.3	dd (pr), (C-8, H-8), 160.0 (C-8, H-6), 7.5	dd, (C-8, H-8), 168.8 (C-8, H-6), 4.1	dd, (C-8, H-8), 161.3 (C-8, H-6), 5.6
9	dd, (C-9, H-9), 156.0 (C-9, H-7), 6.3	dd, (C-9, H-9), 160.0 (C-9, H-7), 6.8	d, (C-9, H-9), 162.5	d, (C-9, H-9), 161.3
9a	t, (C-9a, H-6), 6.9 (C-9a, H-8), 6.9	t, (C-9a, H-6), 5.8 (C-9a, H-8), 5.8	t (pr), (C-9a, H-6), 6.7 (C-9a, H-8), 6.7	t (pr), (C-9a, H-6), 7.5 (C-9a, H-8), 7.5
10	q, (C-10, H-10), 152.0	q, (C-10, H-10), 140.0	q, (C-10, H-10), 150.0	q, (C-10, H-10), 140.0
11	q, (C-11, H-11), 152.0			
1′		t, (C-1′, H-3′), 7.5 (C-1′, H-5′), 7.5	t, (C-1′, H-3′), 7.2 (C-1′, H-5′), 7.2	t (pr), (C-1′, H-3′), 7.5 (C-1′, H-5′), 7.5
2′,6′		dt, (C-2′, H-2′), 162.5 (C-2′, H-4′), 6.3 (C-2′, H-6′), 6.3	dt, (C-2′, H-2′), 168.8 (C-2′, H-4′), 5.9 (C-2′, H-6′), 5.9	dt, (C-2′, H-2′), 162.5 (C-2′, H-4′), 5.6 (C-2′, H-6′), 5.6
3′,5′		dd, (C-3′, H-3′), 160.0 (C-3′, H-5′), 7.5	dd, (C-3′, H-3′), 158.3 (C-3′, H-5′), 9.3	dd, (C-3′, H-3′), 160.0 (C-3′, H-5′), 8.4
4′		dt (pr), (C-4′, H-4′), 160.0 (C-4′, H-2′), 6.3 (C-4′, H-6′), 6.3	dt, (C-4′, H-4′), 168.8 (C-4′, H-2′), 5.9 (C-4′, H-6′), 5.9	dt (C-4′, H-4′), 162.5 (C-4′, H-2′), 5.6 (C-4′, H-6′), 5.6
14				q, (C-14, F-14), 309.8

[a] d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; pr = poor resolution. [b] The splitting pattern is partially obscured by overlap of some phenyl resonances. The 2 bond C-F coupling is not clearly defined in the spectrum of **6**.

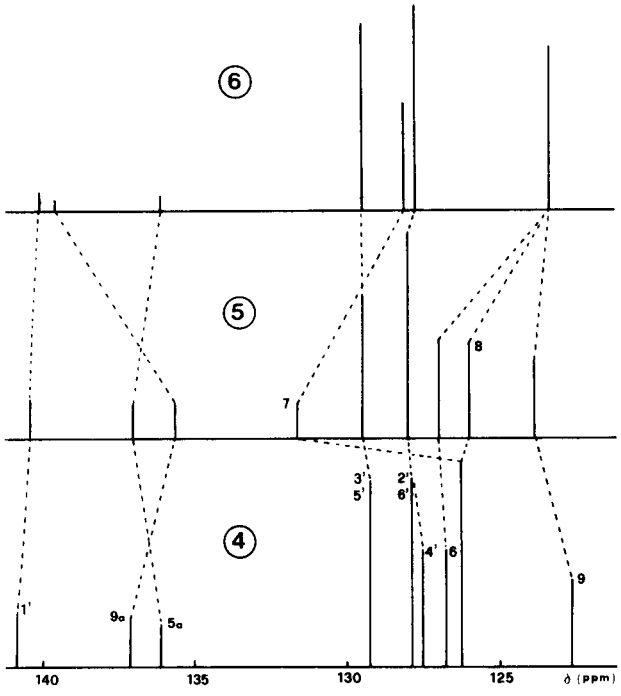

Figure 3. PND ^{13}C Aromatic Resonances for Compounds **4** to **6**.

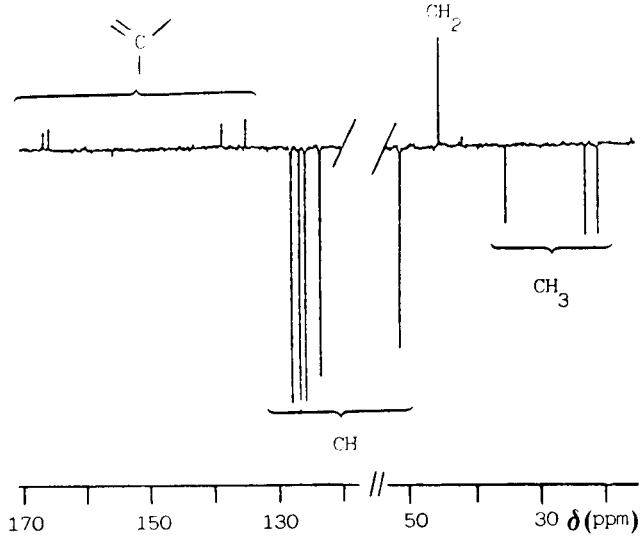

Figure 4. ^{13}C APT Spectrum of 2,3,4,5-Tetrahydro-1-methyl-5-isopropyl-1*H*-1,5-benzodiazepine-2,4-dione (**2**) (singlets and triplets up, doublets and quartets down).

Moving from the aforementioned unequivocal assignments concerning the base compound **1**, the analysis of the spectra for the other five compounds **2** to **6** was carried out in a similar way, the assignments being corroborated by single-frequency off-resonance decoupled (SFORD) spectra, attached proton test (APT) [16] and gated decoupling technique [14b,17] experiments (see experimental) as often as by comparison with the literature data [5-13]. In order to emphasize the usefulness in ^{13}C-nmr spectrum interpretation of APT experiment, from which both the chemical shifts and multiplicities can be determined by acquiring a single spectrum with normal sensitivity, we reproduce in Figure 4 the ^{13}C APT spectrum of compound **2**, which contains all four possible types of carbon resonances.

Generally speaking the six compounds under study (Figure 1) can be divided up into two groups: the 5-alkyl- **1** to **3** and the 5-phenyl-1,5-benzodiazepines **4** to **6**. Between these last products, clobazam (**5**) and triflubazam (**6**) are the most interesting compounds of the series, clinically used as psychotherapeutic agents.

As observed for **1**, the spectra of **2** show separate signals for every carbon in the molecule: the two methyl carbons of the *iso*-propyl group have different resonances, because diastereotopic in consequence of dissymmetry of the molecule on the whole and slow heptatomic ring reversal, compared to the nmr time scale [2c,18]. The nitrogen pyramidal inversion and rotation about C-N bonds should be faster processes than heptatomic ring reversal, as found in 1,3-dihydro-2*H*-1,5-benzodiazepin-2-one derivatives [19].

The shielding of C-4 in **2**, in comparison with C-2, can be taken to reflect the slightly stronger field effect of *iso*-propyl relative to methyl *N*-substituent, which renders the N-5 lone electron pair more available for resonance with the carbonyl group. For analogous reasons, C-4 appears more deshielded than C-2 in the 5-benzyl derivative **3** (reduced availability of N-5 lone pair). Steric effects of N-5 substituents may also contribute to the aforementioned small differences between C-2 and C-4 chemical shifts, observed in compounds **2** and **3**. Moreover, C-2 and C-4 resonances appear more apart the one from the other in 5-phenyl compounds **4** to **6**, owing to the different mesomer and inductive effects of the 1-methyl and 5-phenyl groups; it should be kept in mind that C-2 chemical shift may be influenced also by 7-substituent, *para* to N-1.

On going from **1** to **2**, the comparable shielding of C-9a and deshielding of C-5a are in line with >NR substituent electronic effects on *ipso*- and *ortho*-carbon atoms [14a,15] owing to the enhanced inductive electron release of *iso*-propyl relative to methyl group (Figure 2). Following these arguments, we conclude that the lowest field aromatic signal in PND spectrum of **3** may be due to C-9a, because of the reduced electron-donating effect of benzyl in comparison with methyl substituent.

The assignment of benzyl absorptions in compound **3** is based on the spectral characteristics of benzylamine [20a], taken as model compound, while acetanilide is the selec-

ted model compound for the assignments of phenyl resonances in ^{13}C-nmr spectra of **4** to **6** [5,9,20b].

The differences in the aromatic moieties of ^{13}C-nmr spectra of 5-phenyl-1,5-benzodiazepines **4** to **6** can be similarly rationalized taking into account the effects of both N-5-phenyl and C-7 substitutions (Figure 3). For example, when C-7 is unsubstituted as in **4**, C-9a resonates at lower field than C-5a because of the reduced deshielding of *ipso*-carbon and shielding of *ortho*-carbons respectively, caused by >N-Ph substituent on the aromatic ring, compared with >N-Me. In **5** the chemical shifts of ring junction carbons roughly cross over, because 7-Cl not only strongly deshields (+ 5.33 ppm) the substituted carbon, but also shields the *para* C-9a (− 1.42 ppm) and deshields the *meta* C-5a (+ 0.93 ppm) approximately of the same absolute value [21]. However, C-9a resonates again at lower field than C-5a in ^{13}C-nmr spectrum of compound **6**: in general, the substituent chemical shift pattern observed for the 7-trifluoromethyl substituent in **6**, relative to **4**, appears to be consistent with a substantial π_F effect for the polar part of the substituent effect [22-24].

At the observation temperature and for compounds **4** to **6** 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 phenyl ring about the N-5 to C-1′ axis.

Finally, in all investigated compounds **1** to **6**, C-9 absorptions vary over no more than 1.25 ppm, because almost unaffected by substituent changes, which occur always at N-5 and/or C-7, *i.e.* at *meta*-positions to C-9. For analogous reasons, the C-7 chemical shift values are nearly constant in compounds **1** and **4**, showing no substitution at C-7.

EXPERIMENTAL

2,3,4,5-Tetrahydro-1-methyl-1*H*-1,5-benzodiazepine-2,4-diones **1** to **4** were synthetized as reported by Rossi *et al.* [25]. Clobazam (**5**) was extracted with chloroform from the corresponding drug Frisium^R (Hoechst AG) in a Soxhlet apparatus. Triflubazam (**6**) was kindly furnished by Boheringer Ingelheim S.p.A. All the samples used in ^{13}C-nmr experiments were analytically pure: see CHN elemental analyses in note [26].

The ^{13}C-nmr PND, SFORD and gated decoupling experiments were executed on a Varian FT-80 nmr spectrometer operating at 20 MHz in the Fourier transform mode. The chemical shift values (δ) are expressed in ppm relative to TMS at δ = 0.00 and the coupling constants (J) are expressed in Hertz (Hz). All measurements were carried out for solutions *ca.* 0.2 *M* (10 mm tubes) in deuteriochloroform, which was also used as an internal lock. Both the PND and SFORD spectra of **1** to **6** were recorded, while the gated decoupling technique was used [14b,17] for the coupled spectra of compounds **1**, **4** to **6**. Typical instrument parameters were: spectral width, 5 KHz; acquisition time, 0.819 seconds; pulse width 6 μs (tip angle 30°); 8K (8192) data points were employed in the acquisition of both the decoupled and coupled spectra. For compounds **2**, **3** and **6** the APT experiment [16] was performed on a Varian XL-200 nmr spectrometer operating at 50.3 MHz. Typical instrument parameters in the performance of APT experiment were: spectral width, 11.062 KHz; acquisition time, 1.446 seconds; pulse width, 4.3 μs (tip angle 45°); duration of delays, D1 = 0, D2 = 6, D3 = 1 ms; preacquisition delay, 1 second. The XL-200 nmr spectrometer operates in quadrature phase detection.

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[18] Also the ^{1}H-nmr spectral analysis of compound **2** shows that it exists as only one boat-shaped conformer at room temperature and in deuteriochloroform solution: the 3-CH_2- protons resonate as an AB system centered at δ 3.30 (J_{AB} = 12.4) and the methyl protons of *iso*-propyl substituent resonate as two doublets (δ 1.54 and 1.22, J_{vic} = 7.0).

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[21] The values for 7-Cl substituent effect, placed in parentheses, are calculated from the observed chemical shifts (Table 1) for compounds **4** and **5**, which differ from each other in C-7 substitution only.

[22] The π_F effect arises from a polarization of the π-system by a through-space electrostatic interaction with a remote dipole or charged substituent, see reference 24.

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[26] Compound **1**. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.33; H, 6.02; N, 13.58. Compound **2**. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.49; H, 7.03; N, 11.99. Compound **3**. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.96; H, 5.87; N, 10.10. Compound **4**. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.32; H, 5.18; N, 10.38. Compound **5**. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 64.05; H, 4.30; N, 9.15. Compound **6**. Calcd. for $C_{17}H_{13}F_3N_2O_2$: C, 61.07; H, 3.92; N, 8.38; Found: C, 60.89; H, 3.97; N, 8.46.