^{1}H- and ^{13}C-NMR Spectra of Fenobam

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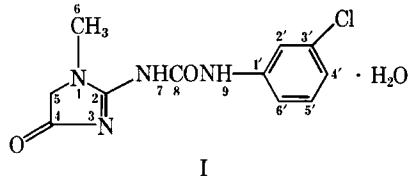
Abstract □ ^{1}H- and ^{13}C-NMR data and spectral assignments are reported for fenobam using noise modulated gated, single frequency off resonance, and single frequency selective proton decoupling techniques.

Keyphrases □ Fenobam—^{1}H- and ^{13}C-NMR spectroscopic analysis □ ^{1}H- and ^{13}C-NMR spectroscopy—analysis of fenobam

Fenobam (I), *N*-(3-chlorophenyl)-*N'*-(4,5-dihydro-1-methyl-4-oxo-1*H*-imidazol-2-yl)urea monohydrate, has been shown to possess selective anxiolytic properties in animals and in clinical trials, with a mode of action different from that of the benzodiazepines (1, 2).



I

NMR parameters, especially ^{13}C-chemical shifts, are being widely used to establish structure–activity relationships. As a part of a study on psychoactive molecules, the ^{1}H- and natural abundance ^{13}C-NMR spectra of I are reported. Their assignments are accomplished by gated, single frequency off resonance, and single frequency selective proton decoupling, and by comparison with other structurally related compounds.

EXPERIMENTAL

The NMR spectra were recorded at room temperature from 0.3 *M* solutions of I in $^2H_6$-dimethyl sulfoxide in 5 mm (^{1}H-NMR) and 10-mm (^{13}C-NMR) tubes[1]. Tetramethylsilane was used as the internal standard for ^{1}H-NMR spectra, while the ^{13}C-multiplet of the deuterated solvent served as the internal reference. Chemical shifts were converted to tetramethylsilane scale using:

$$\delta = \delta\ (^2H_6\text{-dimethyl sulfoxide}) + 39.6\ \text{ppm}$$

^{1}H-NMR spectra were measured at 80 MHz using 90° pulse, sweep widths of 800 and 400 Hz, and single-scan and Fourier transform. ^{13}C-NMR spectra were obtained at 20.1 MHz using 2-μsec pulses (a 90° tip angle required a pulse width of 6.5 μsec), acquisition time 0.9102 sec (corresponding to a sweep width of 4500 Hz), accumulation of free induction decays, and Fourier transform. No delay was given between the end of acquisition and the next pulse. Line broadening (0.5 Hz) was introduced in the spectrum by exponential multiplication of free induction decays. The decoupler was used in broad band, broad band gated, single frequency off resonance, and single frequency selective decoupling modes. Carbon–proton coupling constants were measured from undecoupled spectra and gated proton decoupled spectra.

Monohydrated I was dissolved in $^2H_6$-dimethyl sulfoxide without further purification. A dehydrated sample was prepared by heating at 85° and 1 torr. In the final IR spectrum the water peak disappeared. This sample was dissolved in anhydrous $^2H_6$-dimethyl sulfoxide.

RESULTS AND DISCUSSION

Anhydrous and monohydrated fenobam show identical ^{1}H-NMR spectra. A detailed interpretation of the spectrum was made in order to use single frequency proton decoupling for carbon assignments. The results are presented in Table I.

Table I—Proton Chemical Shifts and Coupling Constants of Fenobam

Protons	δ^a	Hz
5	4.01	—
6	3.00	—
7	9.52[b]	—
9	10.90[b]	—
2′	7.89	—
4′	6.99	—
5′	7.26	—
6′	7.53	—
$J_{H\text{-}2',H\text{-}4'}$	—	2.07
$J_{H\text{-}2',H\text{-}5'}$	—	0.25
$J_{H\text{-}2',H\text{-}6'}$	—	1.99
$J_{H\text{-}4',H\text{-}5'}$	—	7.96
$J_{H\text{-}4',H\text{-}6'}$	—	0.97
$J_{H\text{-}5',H\text{-}6'}$	—	8.60

[a] Parts per million from tetramethylsilane. [b] Values may be interchanged.

The values for the aromatic protons were obtained through iterative simulation[2]. Assignments of H-2′ and H-5′ are straightforward from spectral pattern. The peaks of the multiplet at 7.53 ppm are appreciably broader than those at 6.99 ppm, indicating that the former are due to H-6′ (*ortho* to nitrogen). Assuming additivity in the substituent effect on the aromatic protons chemical shifts and using the values reported previously (3) for the chlorine atom, it turns out from the above assignment that the ureido group has relevant deshielding effects only on the two protons, H-2′ and H-6′, which are in *ortho* positions.

The broad band proton decoupled ^{13}C spectrum consists of 11 well-separated peaks (Table II).

In the gated proton decoupled spectrum, the resonances centered at 30.3 and 51.1 ppm appear as a quartet and a broadened triplet and are attributed to C-6 and C-5, respectively. The resonances centered at 117.1, 118.1 and 121.5 ppm appear as doublets of multiplets reflecting couplings with two *meta* protons and are ascribed to C-6′, C-2′, and C-4′, respectively. In particular, C-4′ originates a doublet of quartets (the two J_{meta} are ~6 and 8 Hz), while the doublet of 1:3:3:1 quartets associated with C-2′ and the doublet of unresolved multiplets assigned to C-6′ indicate a relevant coupling with proton 9. For C-6′, there is also a significant coupling with H-5′. Centered at 130.3 ppm there is a doublet due to C-5′. These assignments are further confirmed by single frequency proton decoupling experiments. The resonances centered at 133.2, 142.3, 157.3, 160.8, and 171.6 ppm belong to quaternary carbons and appear, respectively, as a doublet of unresolved multiplets, another broad doublet, an unresolved multiplet, a slightly broadened singlet, and a triplet.

Selective irradiation of H-2′ causes the complete collapse of the multiplet centered at 118.1 ppm which, therefore, is unambiguously assigned to C-2′. As expected, all the aromatic carbon resonances are strongly affected, *i.e.*, all long-range couplings collapse while the direct C—H bond couplings are strongly reduced in magnitude. The residual splitting decreases in the order C-4′ > C-5′ > C-6′, *i.e.*, as the resonance frequency of the attached proton approaches the decoupling frequency (Table I). This observation and single frequency off resonance experiments support the assignment here reported for C-4′, C-5′, and C-6′. Decoupling of H-2′ has much weaker effects on the resonances at 157.3, 160.8, and 171.6 ppm.

However, irradiation of methylene protons transforms the triplet at 171.6 ppm into a sharp singlet and the unresolved multiplet at 157.3 ppm into a broad singlet, indicating that these resonances are due to imidazolinone ring carbons C-4 and C-2, respectively, the former being coupled only with H-5 protons and the latter with both H-5 and methyl protons. Irradiation of the methyl protons confirms these assignments. Further-

[1] Bruker WP 80 spectrometer equipped with a BNC 28 computer with 8K data memory.

[2] Bruker ITRCAL program.

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Table II—^{13}C-NMR Data

Assignment	δ^a	Multiplicity
C-2	157.3 (169.5[b], 156.7[c])	Unresolved multiplet
C-4	171.6 (188.8[b], 172.0[c])	Triplet, $^2J_{CH}$ = 5 Hz
C-5	51.1 (56.4[b], 54.1[c])	Triplet, $^1J_{CH}$ = 147 Hz
C-6	30.3 (30.2[b], 31.2[c])	Quartet, $^1J_{CH}$ = 140 Hz
C-8	160.8	Singlet
C-1′	142.3	Broad doublet, $^3J_{CH} \simeq 9$ Hz
C-2′	118.1	Doublet of 1:3:3:1 quartets $^1J_{CH}$ = 168 Hz; $^3J_{CH\text{-}4'} \simeq {}^3J_{CH\text{-}6'} \simeq {}^3J_{CH\text{-}9} \simeq 5$ Hz
C-3′	133.2	Doublet of unresolved multiplets, $^3J_{CH} \simeq 11$ Hz
C-4′	121.5	Doublet of quartets, $^1J_{CH}$ = 168.5 Hz, $^3J_{CH} \simeq 6$ and 8 Hz
C-5′	130.3	Doublet, $^1J_{CH}$ = 163 Hz
C-6′	117.1	Doublet of unresolved multiplets, $^1J_{CH}$ = 165 Hz

[a] Chemical shifts in parts per million relative to tetramethylsilane. [b] Values of 2-amino-1,5-dihydro-1-methyl-4*H*-imidazol-4- one. [c] Values for its corresponding monohydrochloride.

more, these decouplings, apart from the collapse of C-5 and methyl carbon resonances, have weak effects on the aromatic carbon resonances, and the splittings due to small C—H couplings are still observable.

The assignment of 142.2 and 133.2 ppm resonances was made by comparison with similar compounds. Assuming that the substituent effects on the shifts of the aromatic carbons are additive and using the data reported previously (4) for the chlorine atom, the values calculated for the ureido group are very close to those determined for other aromatic ureas (5) and acetanilide (4).

The chemical shifts of C-2, C-4, C-5, and C-6 are close to those of 2-amino-1,5-dihydro-1-methyl-4*H*-imidazol-4-one hydrochloride in $^2H_6$-dimethyl sulfoxide (Table II) (6). The ureido ^{13}C-chemical shift (160.8 ppm) is nearer to urea (160.5 ppm) (7) than diphenylurea (152.7 ppm) or di-*p*-anisylurea (153.0 ppm) (5).

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Dissolution Profiles for Finely Divided Drug Suspensions

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Abstract □ A suspension of micronized prednisolone acetate was separated into four fractions by the technique of centrifugal elutriation. Data showed that each fraction had a narrow particle size. The dissolution experiments were carried out under sink conditions (<10% of saturation concentration) in a dissolution apparatus with a rotating filter assembly and a continuous circulation of filtered fluid samples through a recording spectrophotometer. The dissolution profile was highly reproducible and substantially different for each fraction. As expected, fractions with the smallest and largest particles showed the fastest and slowest dissolution, respectively. Almost the entire dissolution profiles for four small particle size fractions can be satisfactorily described by the Higuchi–Hiestand model with the dissolution rate constant, K, in the range of 1.5–2.0 × 10^{-9}cm^2/sec. This is ~3.5 times greater than the value for K calculated on the basis of reported reasonable values for diffusion coefficient, density, and solubility.

Keyphrases □ Dissolution—profiles for drug suspensions, prednisolone acetate, centrifugal elutriation □ Drug suspensions—dissolution profiles, prednisolone acetate, centrifugal elutriation □ Prednisolone acetate—dissolution profiles for drug suspensions, centrifugal elutriation

Dissolution models for multisized drug particles have been proposed and studied experimentally. However, few studies deal specifically with finely divided drug particles (micrometer range). There were notable exceptions (1, 2) published more than a decade ago which showed approximate agreement between diffusional model theory and experimental data for micronized methylprednisolone particles. A more recent study (3) of the dissolution kinetics of micronized steroid particles was unable to confirm the application of the diffusion-based law for the decay of particle size used in those earlier studies (1, 2). To date, the relationship between diffusional-based dissolution theory for finely divided drug particles, and its experimental justification remains fragile.

One of the reasons for the inability to relate the theory with experimental data may be the difficulties encountered in obtaining very small particles with known narrow particle size distributions. The aforementioned studies used multisized drug particle populations in which the dissolution kinetics for the largest and smallest particles may have differed. This possibility has been discussed (4) and an interpolation formula provided which mixes the diffusion kinetics for large and small particles. Therefore, the possibility of mixed models makes critical testing of a specific model difficult. With recent advances in centrifugal elutriation separation and particle size measurement techniques (5) in conjunction with the spin filter dissolution apparatus, it has become possible to test the dissolution models with more rigorously controlled experiments.

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