Nuclear Magnetic Resonance Spectra of Psychotherapeutic Agents. III (1,2). Stereochemistry of 1-Methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2,4-diones

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The stereochemistry of some 1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2,4-diones was determined by proton magnetic resonance using the paramagnetic shift reagent *tris*(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium [Eu(fod)$_3$]; two of these compounds, clobazam and triflubazam, are clinically used as psychotherapeutic agents. Several model structures, with intermediate stereochemistry in the range of the possible limit situations of benzocycloheptene, -cycloheptadiene or -cycloheptatriene type, are considered; LIS (3) are computer simulated on the basis of proton geometric parameters. It was found that at room temperature, these derivatives exist in only one pseudo-boat cycloheptadiene-like conformation, showing the 5-phenyl group directed pseudo-axially. This conformational preference is interpreted in terms of a balance between the steric requirements of the bulky substituent and electronic repulsion in the ring π-system.

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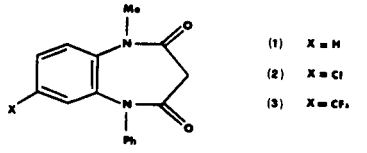
The title compounds (**1-3**) were found to possess important psychopharmacological properties (5), especially when an electronegative substituent is present at the 7-position, as in the most interesting compounds of the series, clobazam (**2**) and triflubazam (**3**) (see Scheme).



Scheme: 1-Methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2,4-diones under Investigation

In order to contribute to a better understanding of the relationship between molecular structure and biological activity in the field of psychotherapeutic agents, we have undertaken the study of the stereochemistry of the title compounds in solution, using the ^{1}H nmr-LIS method (3,6). Results concerning conformational preferences of biologically active substances in solution seems significant, because the preferred conformation may be assumed to approximate the one which exists in the aqueous environment of biological tissue. The stereochemical requirements of the 1,5-benzodiazepine-2,4-diones agree well with our previous results concerning ^{1}H nmr spectra and structure activity relationships of such psychotherapeutic agents as 2,3-dihydro-1*H*-1,4-benzodiazepines (7) and 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (6).

Results and Discussion.

The stereochemical problem of the title compounds is quite complex, because of the presence of two amide groups in the heptatomic ring. The nitrogen atoms at positions 1 and 5 may assume sp^2 hybridization, and the heterocyclic ring may simulate a boat-shaped cycloheptatriene structure, with a possible conformational equilibrium existing between the two enantiomers. However, owing to the different mesomer and inductive effects of the 1-methyl and 5-phenyl substituents, a different stereochemistry for the nitrogen atoms is possible. In this latter case both cycloheptadiene-like and intermediate structures are to be considered. Finally, chair cycloheptene-like structures (8) with both nitrogen atoms being sp^3 cannot be ruled out. The aforementioned cycloheptadiene- or cycloheptene-like structures all involve possible conformational equilibria between the dia-

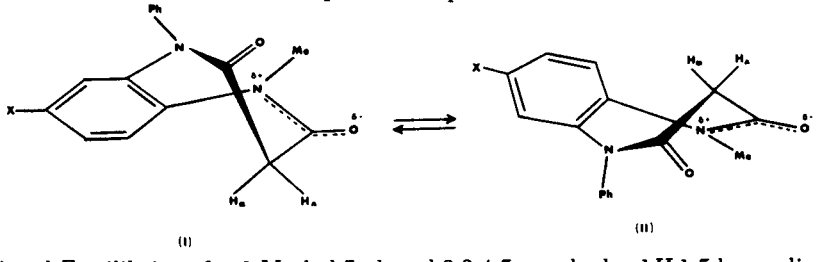


Figure 1: Conformational Equilibrium for 1-Methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2,4-diones (**1-3**)

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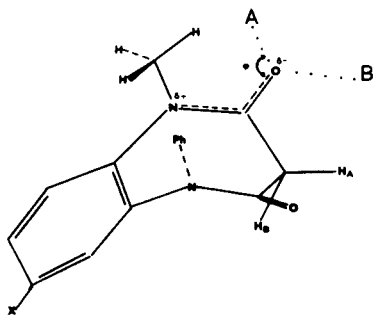

Figure 2: Eu(fod)$_3$ Complexation Sites (A and B) in the 2-Carbonyl Plane

stereomers. Eventual enol forms are not considered because of the absence of hydroxyl absorptions in the ^{1}H nmr and ir spectra, under the adopted experimental conditions.

The paramagnetic shift reagent Eu(fod)$_3$ (LSR) (9) was used to determine the exact stereochemistry of the 1,5-benzodiazepinediones in solution. A reasonable average geometry for the substrate may be deduced by the use of the McConnell-Robertson equation (10) [$\Delta\nu_i = K(3\cos^2\chi_i - 1)r_i^{-3} = KG_i$] which correlated the pseudo-contact lanthanide induced shifts ($\Delta\nu_i$) with the geometrical parameters of the complex, and thus of the substrate. The theoretical LIS in the different aforementioned structures were computer simulated. The actual molecular geometry was assumed to be the one which best fit the observed and calculated LIS. The acceptability of the results was evaluated in terms of the agreement factor AF (11) (AF = $[\Sigma_i(\Delta\nu_{i,obs} - \Delta\nu_{i,calcd})^2/\Sigma_i(\Delta\nu_{i,obs})^2]^{1/2}$), where $\Delta\nu_{i,obs}$ and $\Delta\nu_{i,calcd}$ are the observed and calculated shifts, respectively.

The geometric parameters for the protons in the possible conformations of the different model structures were calculated using standard bond lengths, bond angles and dihedral angles, as estimated from Drieding models. The 1-substituent was treated as a point methyl group (*i.e.*, rotational averaged positions).

Both oxygen atoms may be possible binding sites for europium upon addition of the shift reagent. However, in the compounds examined, only complexation at the 2-carbonyl group was found to contribute appreciably to the observed LIS (see Experimental). These findings correspond to a greater basicity of the oxygen atom in the 2-carbonyl group, owing to the electron-donating effect of the 1-methyl group and the steric situation of the nitrogen atom at the 5-position (*vide infra*). A topological approach to the LSR interaction with the carbonyl group (12) has been adopted, following the simplifying assumption that the lanthanide only occupies chemically accessible sites (lone pairs) at the 2-carbonyl group. These two positions A and B in the 2-carbonyl plane are diastereomeric, as indicated by values of ϕ = 140° and 220°, respectively, where ϕ is the Eu-O-2C angle (the lanthanide-oxygen internuclear distance is 3 Å). The mole fractions of the two diastereomeric complexed substrates were determined by matching the observed LIS values with those calculated for each hydrogen atom according to the following formula:

$$\Delta\nu_{i,obs} = K(W_AG_A + W_BG_B),$$

where W_A and W_B are the mole fractions, G_A and G_B are the geometric factors corresponding to the form with the lanthanide in positions A and B, respectively, and K is the pseudo-contact constant of the McConnell-Robertson equation.

The ^{1}H nmr spectral analysis of compounds **1-3** shows that they exist as only one conformer at room temperature; the methyl and methylene resonances are quite coincident in deuteriochloroform, with the 3-CH_2- resonating as an AB system (J_{AB} in the narrow range of 13 Hz). The addition of the paramagnetic reagent produces the expected

Table (a)

Chemical Shifts, Measured and Simulated LIS for some 1-Methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2,4-diones

Compound No.	H_A	H_B	CH_3	6-H	K (b)	W_A (b)	AF
1	3.49	3.46	3.52		123, 523	0.12	0.023
	13.50	7.31	6.76				
	13.32	7.65	6.75				
2	3.50	3.47	3.50	6.96	123, 595	0.22	0.023
	12.97	7.13	7.40	2.47			
	12.85	7.41	7.40	2.23			
3	3.56	3.54	3.57		103, 600	0.20	0.015
	10.93	6.05	6.14				
	10.83	6.24	6.13				

(a) Figures in the first row indicate chemical shifts (δ) of undoped spectra; figures in the second row indicate the observed molar induced shifts; figures in the third row indicate calculated molar induced shifts. (b) For definitions, see text.

resonance shifts. The obtained LIS are comparable for H_B and methyl, higher for H_A and considerably smaller for the aromatic protons (H_A resonates at lower field than H_B, which is shielded by the fused benzene ring; see Table).

The results of the computer analysis of the observed LIS show that in solution, the real stereochemistry of the preferred conformer of **1-3** is the one depicted in Figure 1 as II. It approximates a pseudo-boat cycloheptadiene-like structure of the heterocyclic ring with sp^2 hybridization of the nitrogen atom at the 1-position, while the nitrogen atom at the 5-position deviates from trigonal stereochemistry to a flattened pyramidal structure. These results have been obtained by comparison of the AF calculated for various conformers of **1-3**, with simulated geometrical features of the 1- and 5-nitrogen atoms intermediate between the limit situations (trigonal or pyramidal nitrogen atoms). The minimum AF for all of the examined compounds corresponds to an elevation of the 5-nitrogen atom in the range of 0.2 Å, from the plane defined by the three atoms bonded to it (6). The interconversion between I and II under the adopted experimental conditions can be excluded, because only the conformer II was detected in different solvents, at the nmr time scale, and in the presence of LSR. The values of the mole fractions W_A for compounds **1-3** reflect that the LSR complexation occurs preferably in the less sterically hindered position (Figure 2).

Noteworthy, the preferred conformer (II) shows a pseudoaxial orientation of the 5-phenyl group. The corresponding 5-nitrogen atom lone pair is pseudoequatorially directed, thus allowing its interaction with the 5-phenyl π-system, rather than with the corresponding electron system of the 4-carbonyl group. This situation agrees with the experimental results concerning the lanthanide complexation, which occurs almost exclusively at the 2-carbonyl group.

Various attractive and repulsive interactions in the ring appear to be of considerable importance in controlling conformation; the observed conformational preference of the 5-substituent may be determined by the balance between the steric requirements of the phenyl group and the electronic repulsions among the 5-lone pair of electrons and the 1,2-amide π-system. These interactions reduce the equatorial preference of the phenyl group, in such a way that the conformer II is preferred. Another possible explanation is that a pseudoaxially oriented 5-lone pair of electrons should interact with the π-systems of both the aromatic rings. However, these favourable electronic interactions are counterbalanced and overcome by the steric hindrance which exists between 6-H and the *ortho*-hydrogen atoms of a pseudoequatorially oriented 5-phenyl group. Thus, the pseudoaxial substituent orientation is favoured on the whole.

In conclusion, the existence of conformation II in deuteriochloroform solutions in compounds **1-3** was established. The greater stability of II renders it possible as the biologically active conformation which exists under the conditions of the action of the drug. However, the torsional angle of the pseudoaxially oriented 5-phenyl group and its potential influence on the biological activity remains to be examined (13). The presence of an electronegative substituent at the 7-position, which is essential for optimal activity of both 1,5-benzodiazepine-2,4-diones and 1,4-benzodiazepines, does not result in a notable modification of the conformational preference in solution.

The results obtained concerning the stereochemistry of the benzodiazepinediones in this study agree well with our previous findings (6) that a generally increased biological activity of many psychotherapeutic benzodiazepine derivatives may be ascribed to the existence, in solution, of a single conformer, which does not interconvert at room temperature.

EXPERIMENTAL

1-Methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2,4-dione (**1**) was synthetized as reported by Rossi, *et al.* (14). Clobazam (**2**) was extracted from the corresponding drug Frisium® (Hoechst AG) with chloroform in a Soxhlet apparatus. Triflubazam (**3**) was kindly furnished by Boheringer Ingelheim S.p.A.

The ir spectra were determined in deuteriochloroform solutions with a Perkin-Elmer Model 257 spectrometer.

The ^1H nmr spectra were obtained at 60 MHz (Varian T60A) at a probe temperature of 34°, for solutions *ca.* 0.3*M* in deuteriochloroform (TMS as internal standard) containing increasing amounts of $Eu(fod)_3$ up to a value of 0.4 moles of ligand (L) per mole of substrate (S). Europium (III) 7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-4,6-octandionate [$Eu(fod)_3$] was purchased from B. H. Schilling. The lanthanide shift reagent was added stepwise from a stock solution (*ca.* 300 mg./ml.) using a 50 µl. syringe. Each signal was followed and the LIS were found to be directly proportional to the L/S ratio present. A least-squares fit for the experimental points was used to obtain the observed molar LIS. Calculations relative to the simulation of the experimental LIS data were performed on an IBM 370/115 computer, using the topological program for the LSR interaction with the carbonyl group (12).

A modification of the topological program was performed in our laboratory to consider the interaction of LSR with both carbonyl groups. The calculated AF were strictly comparable to those obtained taking into account the complexation at the 2-carbonyl group only.

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REFERENCES AND NOTES

(1) For papers I and II, see References 7 and 6.

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(3) LIS = lanthanide-induced proton chemical shifts, see Reference 4.

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