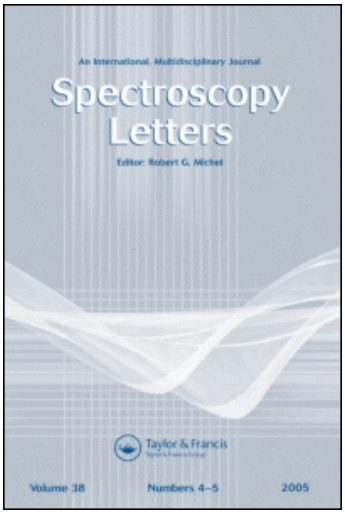


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# Determination of the Stereochemistry of Substituted 5-Methylenehydantoins and Thiohydantoins by $^{13}C$ NMR and Homonuclear NOE Experiments

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# DETERMINATION OF THE STEREOCHEMISTRY OF SUBSTITUTED 5-METHYLENEHYDANTOINS AND THIOHYDANTOINS BY $^{13}C$ NMR AND HOMONUCLEAR NOE EXPERIMENTS

**Key Words** : Methylenehydantoins, methylenethiohydantoins, $^{1}H$ NMR spectra, $^{13}C$ NMR spectra, Homonuclear NOE, C-H coupling constants.



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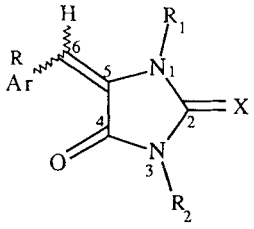
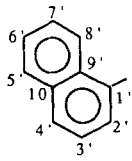
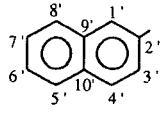
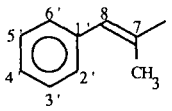
## ABSTRACT

Basically the aim of this work is to define the accurate configuration of the exocyclic double bond of substituted 5-methylenehydantoins and thiohydantoins which have been conceived as potential Aldose Reductase inhibitors. A previsional survey based upon the chemical shifts analysis from $^{1}H$ and decoupled $^{13}C$ NMR spectra discloses, for a part of the family of compounds, the assignment of the *Z*-configuration for unsubstituted (**2,3**) and N-3 substituted (**6,7,9**) derivatives, and the *E*-configuration for the N-1 substituted (**8,11**) ones. The qualitative study with Homonuclear NOE (**8,11**) and the coupling constant measuring $^{3}J_{C_4\text{-}C=C\text{-}H_6}$ from coupled $^{13}C$ NMR (**1-11**), lead to the assignment of the accurate configuration of the whole family's compounds in agreement with the previsional study.

**TABLE 1 : Structure of 5-Methylenehydantoins and Thiohydantoins.**

| General structure | $R_1, R_2$ : H, $CH_2$-COOH | | |
|---|---|---|---|
|  | Methylene substituants | | |
| | Ar : 1-naphtyl | Ar : 2-naphtyl | R : 2-methylcinnamyl |
| |  |  |  |
| | X : O, S | | |



## INTRODUCTION

New Aldose Reductase (AR) inhibitors conception has been developed, throughout the last few years, as an approach to the treatment of diabetic complications : cataract, retinopathy, nephropathy and neuropathy[1-3]. Few known AR inhibitors as Sorbinil[4]: *(S)*-6-Fluoro-2,3-dihydrospiro[*4H*-1-benzopyran-4,4'-imidazolidine]-2',5'-dione, and Epalrestat[5] : *(E,E)*-5-(2-methyl-3-phenyl-2-propenyliden)-4-oxo-2-thioxo-3-thiazolidineacetic acid, have revealed a potent inhibitory activity, clinically demonstrated[1-3,6], and have been used as patterns to conceive a new class of AR inhibitors. From the structural models, we focused our attention on hydantoins and 2-thiohydantoins derivatives, which may present acidic properties.

They are synthesized from aromatic aldehyde condensed with substituted or unsubstituted hydantoins and 2-thiohydantoins, in acetic acid in the presence of sodium acetate [7-9] (TABLES 1 and 2).

TABLE 2 : Synthesized compounds.

| Compound | Ar | $R_1$ | $R_2$ | X |
|---|---|---|---|---|
| 1 | 1-naphtyl | H | H | O |
| 2 | 2-naphtyl | H | H | O |
| 3 | 2-naphtyl | H | H | S |
| 4 | 1-naphtyl | H | $CH_2$-COOH | O |
| 5 | 1-naphtyl | H | $CH_2$-COOH | S |
| 6 | 2-naphtyl | H | $CH_2$-COOH | O |
| 7 | 2-naphtyl | H | $CH_2$-COOH | S |
| 8 | 2-naphtyl | $CH_2$-COOH | H | O |
| 9 | 2-méthylcinnamyl | H | $CH_2$-COOH | O |
| 10 | 2-méthylcinnamyl | H | $CH_2$-COOH | S |
| 11 | 2-méthylcinnamyl | $CH_2$-COOH | H | O |



The study's purpose consists in the stereochemical determination of the exocyclic double bond of these compounds. In effect, $^1H$ and $^{13}C$ NMR spectra do not permit to elucidate the *Z/E* configuration. On the other hand, Homonuclear NOE (Nuclear Overhauser Effect) and coupled $^{13}C$ NMR spectra acquisition with proton selective irradiation have been helpful to achieve a configurational study. The assigned configurational results should help the analysis of pharmacological experiments.

## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were recorded at 20°C, in DMSO-$d_6$ solutions in 5 mm tube on a Bruker AC 200 spectrometer with a proton operating frequency of 200.13MHz and referenced to the solvent signal.

The following parameters were used :

- For proton spectra : data points, 16K; spectral width, 2200Hz; pulse angle, 60°; acquisition time, 3.7s.
- For noise-decoupled carbon spectra : data points, 16K; spectral width, 11140Hz; pulse angle, 45°; acquisition time, 0.7s; pulse delay, 0.8s.

**TABLE 3 : Chemical Shifts δ $^{1}H$ (ppm).**

| Compound | Aromatic | | Vinyl | | $CH_2$ | $CH_3$ | COOH |
|---|---|---|---|---|---|---|---|
| | $H_{1'}$ | $H_{3'}$ | $H_6$ | $H_8$ | | | u : unseen |
| 1 | - | - | 6.99 | - | - | - | - |
| 2 | 8.21 | 7.70 | 6.56 | - | - | - | - |
| 3 | 8.36 | 7.78 | 6.62 | - | - | - | - |
| 4 | - | - | 7.08 | - | 3.88 | - | 10.76 |
| 5 | - | - | 7.26 | - | 4.50 | - | u |
| 6 | 8.27 | 7.74 | 6.74 | - | 4.23 | - | 11.15 |
| 7 | 8.43 | 7.85 | 6.83 | - | 4.52 | - | 12.70 |
| 8 | 8.34 | 8.10 | 6.66 | - | 4.48 | - | 11.60 |
| 9 | - | - | 6.33 | 6.92 | 4.15 | 2.16 | 10.55 |
| 10 | - | - | 6.14 | 6.62 | 4.02 | 1.94 | u |
| 11 | - | - | 5.90 | 6.80 | 3.80 | 2.17 | 11.18 |

**TABLE 4 : Chemical Shifts δ $^{13}C$ (ppm).**

| Compound | Vinyl | | | $CH_2$ | $CH_3$ | $C_4$=O | $C_2$=O | $C_2$=S | C=O |
|---|---|---|---|---|---|---|---|---|---|
| | $C_8$ | $C_7$ | $C_6$ | | | amide | urea | thiourea | acid |
| 1 | - | - | 104.5 | - | - | 165.3 | 155.7 | - | - |
| 2 | - | - | 108.3 | - | - | 165.6 | 155.8 | - | - |
| 3 | - | - | 111.6 | - | - | 165.8 | - | 179.3 | - |
| 4 | - | - | 105.2 | 41.5 | - | 163.8 | 155.3 | - | 169.0 |
| 5 | - | - | 110.0 | 42.2 | - | 163.3 | - | 178.6 | 168.4 |
| 6 | - | - | 110.3 | 39.4 | - | 163.7 | 154.6 | - | 168.7 |
| 7 | - | - | 113.6 | 41.9 | - | 163.6 | - | 178.4 | 168.2 |
| 8 | - | - | 116.1 | 40.8 | - | 162.8 | 153.7 | - | 169.2 |
| 9 | 136.1 | 125.5 | 116.0 | 39.3 | 16.9 | 163.7 | 154.4 | - | 168.8 |
| 10 | 136.9 | 128.4 | 117.4 | 44.2 | 17.2 | 164.8 | - | 178.9 | 168.8 |
| 11 | 134.1 | 129.7 | 120.0 | 43.6 | 18.6 | 162.7 | 153.6 | - | 168.9 |

**TABLE 5 : Configurational Prevision of Oxygenated Cinnamyl and 2-Naphtalenyl Compounds from $^1H$ Spectra.**

| Compounds | Proton | $\delta$ $^1H$(ppm) | Relative effect | Relative spatial position of $C_4 = O$ | Expected configuration |
|---|---|---|---|---|---|
| 2,3,6,7 | $H_{3'}$ | 7.70 - 7.85 | shielding | distant | *Z* |
| **8** | | 8.10 | deshielding | close | *E* |
| **9** | $H_6$ | 6.33 | deshielding | close | *Z* |
| **11** | | 5.90 | shielding | distant | *E* |

- For coupled carbon spectra with/without proton selective decoupling : Bruker's programs as SFDEC (with selective irradiation) and GATEDEC (coupled $^{13}C$ spectra).

## RESULTS AND DISCUSSION

Necessary chemical shifts for the configurational study are reported in TABLES 3 and 4.

### 1) Configurational Prevision

Differences in proton ($H_{3'}$ and $H_6$) and carbon ($C_2$ urea, $C_4$ amide, acid) chemical shifts are noted from $^1H$ and $^{13}C$ NMR spectra analysis concerning the studied family excepted compounds **1**,**4** and **5**.

For the $H_{3'}$ and $H_6$ protons, the anisotropic effect of the 4-carbonyl group, depending upon its relative position with the protons, produces a deshielding of the proton $H_{3'}$ in the compound **8** and the $H_6$ proton in the compound **9**. This variation of chemical shifts permits the *Z*/*E* configurational forecast of the named compounds (TABLE 5 ).

Concerning the cinnamyl derivatives, the comparison of $H_6$ proton chemical shifts of compound **10**, alone with its sulphur

**TABLE 6 : Configurational Prevision of Oxygenated Cinnamyl and 2-Naphtalenyl Compounds from $^{13}C$ Spectra.**

| Compounds | Carbons $\delta$ $^{13}C$(ppm) | | | Expected configuration |
|---|---|---|---|---|
| | $C_2$ urea | $C_4$ amide | $C_6$ vinyl | |
| **8,11** | 153.6 - 153.7 | 162.7 - 162.8 | 116.0 - 120.0 | *E* |
| **2,3,6,7,9** | 154.4 - 155.8 | 163.3 - 165.8 | 104.5 - 117.4 | *Z* |



character, with compound **9** and **11** cannot be valid for a configurational prevision of **10**.

Previous data, concerned by a part of the whole family of compounds, which present a relative aspect, require more investigations to assign the exact configuration of the exocyclic double bond.

On the other hand, S.F.Tan and al.[9], have noticed, the $C_2$ urea and $C_4$ carbons resonate downfield and the $C_6$ carbon upfield respectively in *Z*-isomers, comparatively to *E*-isomers. Such a variation in the same range reported in TABLE 6 are considered for hydantoins derivatives, coherently with mentioned previsional analysis in TABLE 5.

## 2) Configurational Study

From the basic structure of these compounds, a configurational study can be achieved thanks to the knowledge of some other acquired parameters:

- Presence or absence of Homonuclear NOE, with N-1 substituted derivatives,

- Coupling constant measuring between the vinyl $H_6$ proton and the $C_4$ amide carbon.

### a) Configurational Study with Homonuclear NOE

This kind of study concerns compounds which show spatially close protons, in one configuration or the other : the vinyl $H_6$ proton and the protons of methylene group (compounds **8** and **11**).

This study cannot be done with unsubstituted and N-3 substituted derivatives, which do not offer the required context.

Experiments emphasize significant Homonuclear NOE between the involved protons, suggesting the exact *E* -configuration in compounds **8** and **11** (TABLE 7).



### b) Configurational Study with Coupling Constant Measurement

Since the configurational study with Homonuclear NOE experiments cannot be achieved with unsubstituted and N-3 substituted derivatives, another field of investigation is considered.

These structures present a vinyl $H_6$ proton and a $C_4$ amide carbon placed in the *cis/trans* configuration to the studied double bond.

Previous works achieved with compounds presenting the same basic structures (Ishida[8], Vögeli[10]) have revealed the variations of the vicinal coupling constant $^3J_{\underline{C}_4\text{-}C=C\text{-}\underline{H}_6}$ in the range of 3.7 - 6.8 Hz for the *cis* configuration and 10.0 - 12.3 Hz for the *trans* one. Experiments in coupled $^{13}C$ NMR with selective irradiation of methylene protons lead to the measuring of the coupling constant.

The assignment of the $C_4$ amide, $C_2$ urea, and acid carbons' resonances is a result of the analysis of their magnetic environment

TABLE 7 : Homonuclear NOE Effect (δ ppm)

| Compound | Irradiated proton (δ $^1$H) | Affected proton by NOE effect (δ $^1$H) |
|---|---|---|
| 8 | $H_6$ (6.66) | $CH_2$ (4.48)<br>$H_{1'}$ (8.38)<br>$H_{3'}$ (8.10) |
| | $CH_2$ (4.48) | $H_6$ (6.66) |
| 11 | $H_6$ (5.90) | $H_9$ (6.80)<br>$CH_2$ (3.80) |
| | $H_9$ (6.80) | $H_7$ (5.90) |



(TABLE 4) and the comparison of the signals' multiplicities before and after the selective irradiation (TABLES 8 and 9). Within N-3 substituted derivatives, the multiplicity of the $C_4$ amide carbon signal is so large, that the coupling constant measurement cannot be realized under these conditions. Only selective irradiations lead to a simplified signal and a determination of the coupling constant.

After selective irradiation of vicinal protons, the signal of the $C_4$ amide carbon seems like:

- an unachieved multiplet, with a better resolution resulting of a selective irradiation of the $H_6$ proton.
- a doublet or a double doublet, obtained by selective irradiation of the methylene protons -$CH_2$-, leading to the coupling constant's value (TABLE 9).

Concerning unsubstituted and N-1 substituted derivatives, the signal's multiplicity of the $C_4$ amide carbon is weaker; consequently the coupling constant will be directly measured in coupled $^{13}C$ spectra (TABLE 9).

**TABLE 8 : Multiplicities of Carbonyl Groups**

| Compounds | $C_4$ amide carbon | | $C_2$ urea carbon | | acid carbon | |
|---|---|---|---|---|---|---|
| | Coupled $^1H$ | multiplicity | Coupled $^1H$ | multiplicity | Coupled $^1H$ | multiplicity |
| unsubstituted **1-3** | $H_6$ ($J_1$) | d | - | s | - | - |
| N-1 substituted **8,11** | $H_6$ ($J_1$) | d | $C\underline{H}_2$ ($J_2$) | t | $C\underline{H}_2$ ($J_2$) | t |
| N-3 substituted **6,9** | $H_6$ ($J_1$) $C\underline{H}_2$ ($J_2$) $N_1\underline{H}$ ($J_3$) | tdd | $C\underline{H}_2$ ($J_2$) | t | $C\underline{H}_2$ ($J_2$) | t |
| **4,5,7,10** | $H_6$ ($J_1$) $C\underline{H}_2$ ($J_2$) | td | $C\underline{H}_2$ ($J_2$) | t | $C\underline{H}_2$($J_2$) | t |

**TABLE 9 : Signal's Multiplicities of $C_4$ Carbon with/without Selective Irradiation and Coupling Constants**

| Compound | Coupled $^{13}C$ with/without irradiation of $CH_2$ protons (yes/no) | Obtained $C_4$ carbon's multiplicity | $^3J_{C_4\text{-}C=C\text{-}H_6}$ (Hz) | Deduced configuration |
|---|---|---|---|---|
| **1** | no[a] | d | 5.73 | Z |
| **2** | no[a] | d | 5.84 | Z |
| **3** | no[a] | d | 5.28 | Z |
| **4** | yes | d | 5.81 | Z |
| **5** | yes | d | 5.39 | Z |
| **6** | yes | dd or t | 6.33 | Z |
| **7** | yes | d | 5.62 | Z |
| **8** | no | d | 10.78 | *E* |
| **9** | yes | dd or t | 7.26 | Z |
| **10** | yes | d | 5.13 | Z |
| **11** | no | d | 10.04 | *E* |

a : $-CH_2-$ group absent.

## CONCLUSION

Basically the aim of this study is to define the exact configuration of the exocyclic double bond within the proposed compounds. A previsional survey has been undertaken from the $^{1}H$ and $^{13}C$ spectra analysis. The qualitative study with Homonuclear NOE effect and the coupling constant measuring achieved with/without selective irradiation of proton, lead to the assignment of the accurate configuration and reveal a good coherence with the previsional study.

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## REFERENCES

1. Kador P.F., Kinoshita J.H., Sharpless N.E. Aldose Reductase Inhibitors: A Potential New Class of Agents for the Pharmalogical Control of Certain Diabetic Complications. J.Med.Chem.,1985, 28, 841-9.

2. Lipinski C.A., Hutson N.J. Chapter 17. Aldose Reductase Inhibitors as a new approach of the treatment of diabetic complications. Annu. Rep. Med. Chem. 1984, 19, 169-77.

3. Mutschler E., Winterfeldt E. Aldose Reductase Inhibitors. Trends in Medicinal Chemistry. VCH 1987; 9th Symposium, Berlin, 1986, 551-564.

4. Sarges R. G.pat.2,821,966 (1978), U.S.pat.4,130,714 (1978).

5. Tadao T., Masanori K., Akio A., Tetsuya M., Masaki H., Hiroshi T., Fumio H., Takeshi M. ONO Pharm.Co., Ltd, EP 47,109 (1982), U.S.pat.4,464,382 (1984).

6. Epalrestat. Drugs in the Future, 1987, 12 (4), 336-40.

7. Wheeler H.L., Hoffmann C. On hydantoins: a synthesis of phenylalanine and of tyrosine. Am.Chem.J.,1911,45, 368-83.

8. Ishida T., In Y., Inoue M., Ueno Y., Tanaka C. Structural Elucidation of Epalrestat (ONO-2235), A Potent Aldose Reductase Inhibitor, and isomerisation of its double bonds. Tetrahedron Letters. 1989, 30(8),959-62.

9. Tan S.F., Ang K.P., Fong Y.F. *(Z)*- and *(E)*-5-Aryl methylidene hydantoins: Spectroscopic Properties and Configuration Assignment. J.Chem.Soc.Perkin Trans. II,1986,1941-46.

10. Vögeli V., Philipsborn W., Nagarajan K., Nair M.D. Structures of Addition Products of Acetylenedicarboxylic Acid Esters with Various Dinucleophiles. An Application of C,H-Spin-Coupling Constants. Helv.Chim.Acta, 1978, 61(2), n°49, 607-17.

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