MYSTERIOUS NEGATIVE PEAKS IN THE ¹H{¹H} NOE DIFFERENCE SPECTRA OF SOME THIOPYRAN COMPOUNDS

Csaba Szántay, Jr.

**Chemical Works of Gedeon Richter Ltd.
H-1475, Budapest, POB 27, Hungary.**

Thioyrans 1-4 were formed in the course of regiospecific and stereoselective Diels-Alder cycloadditions involving 2-(N-Acylamino)-1-thia-1,3-dienes. The constitution and the main conformational features of thiopyrans 1 - 4 were established using classical high field NMR methods: 2D ¹H-¹H and ¹³C-¹H shift correlation, selective ¹³C{¹H} and ¹H{¹H} NOE difference experiments [1], [2].

1   **2**   **3**   **4**
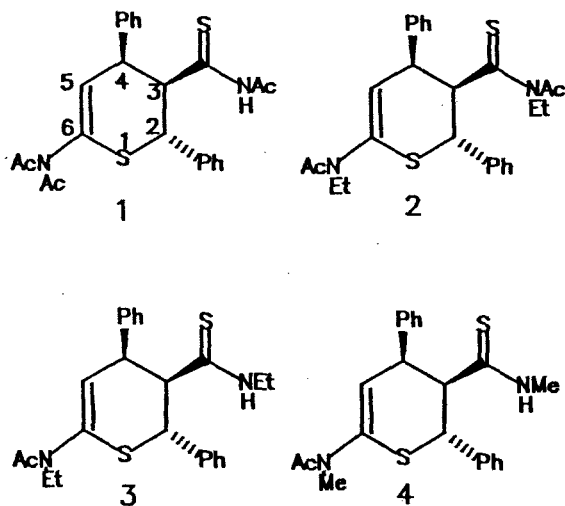
Conformational aspects:

a) ring pseudorotation:

In the case of compounds **3** and **4** the thiopyran ring exhibits a slow ring flip between the relevant half-chair forms. This gives rise to saturation transfer effects in the ¹H{¹H} NOE difference experiments, as illustrated for **4** in Fig. 1.

In **1** and **2** the ring conformational equilibrium is completely shifted towards the form in which H-2 and H-3 are antiperiplanarly arranged (Fig. 2).

b) The C(3) sidechain:

The sidechain shows free rotameric mobility at room temperature. The conformational features were characterized in terms of the measured NOEs and MM calculations [1]. The relative contributions of the major sidechain conformations are depicted in Fig. 2.
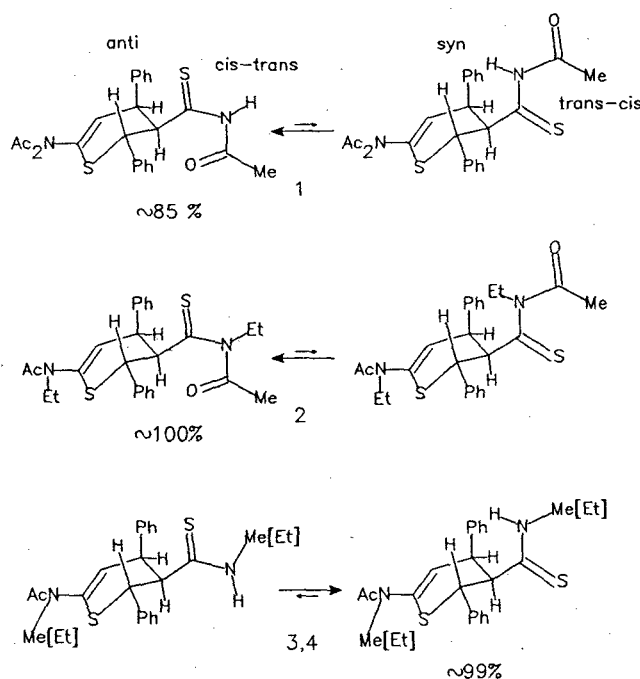

Figure 2. The main rotameric forms of the C(3) sidechain in compounds **1-4**.
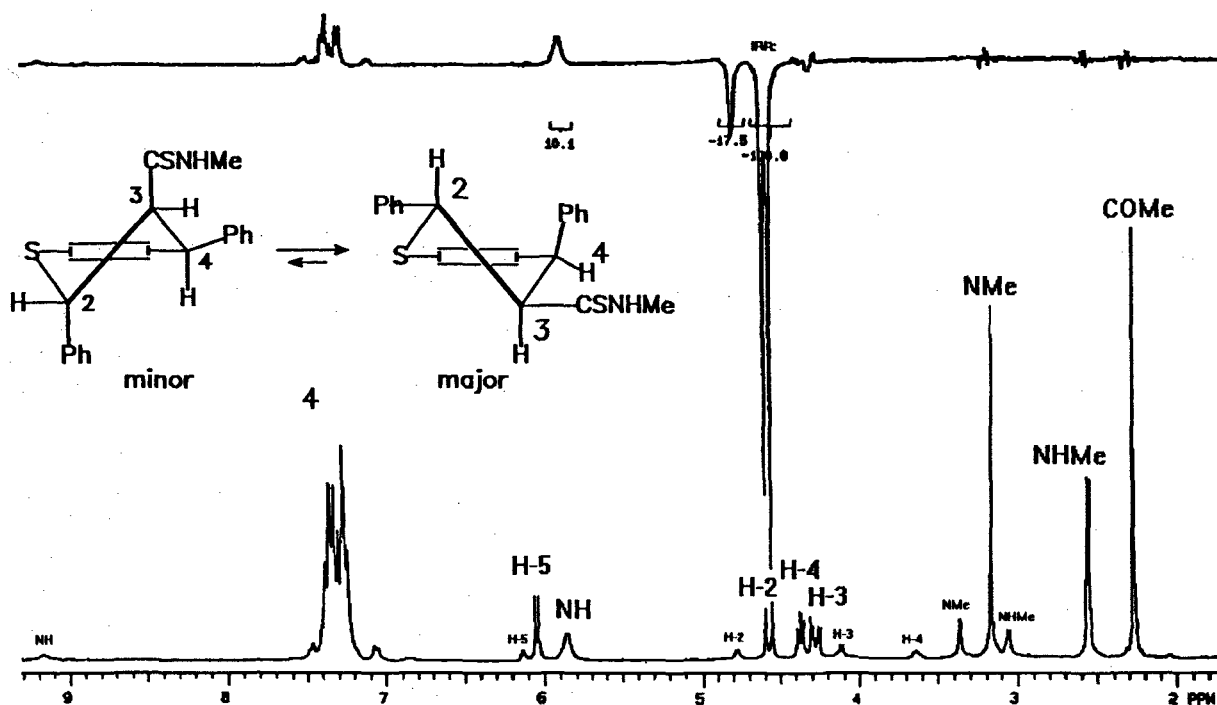
Figure 1. One of the several NOE difference spectra of compound **4** showing the presence of saturation transfer as a result of a slow ring interconversion.
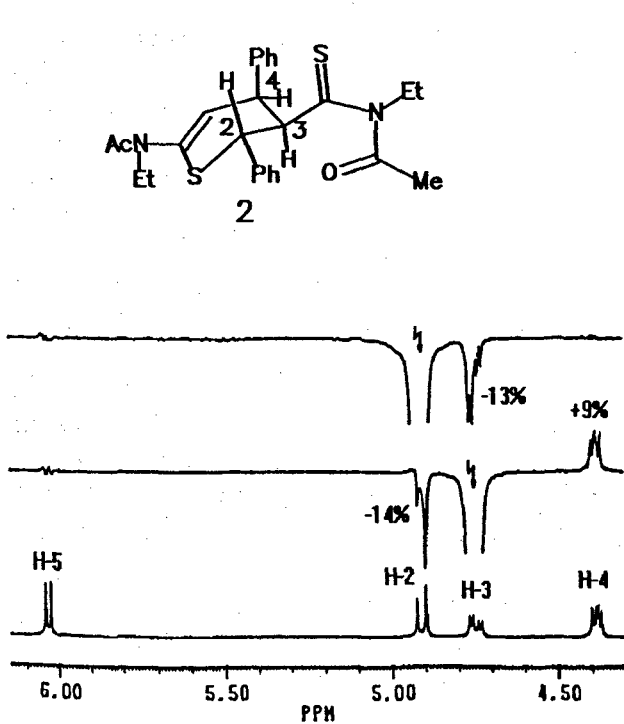

Figure 3. A segment of the NOE difference spectra showing negative peaks in the case of **2**. (CDCl₃, 25 °C, 400 MHz).
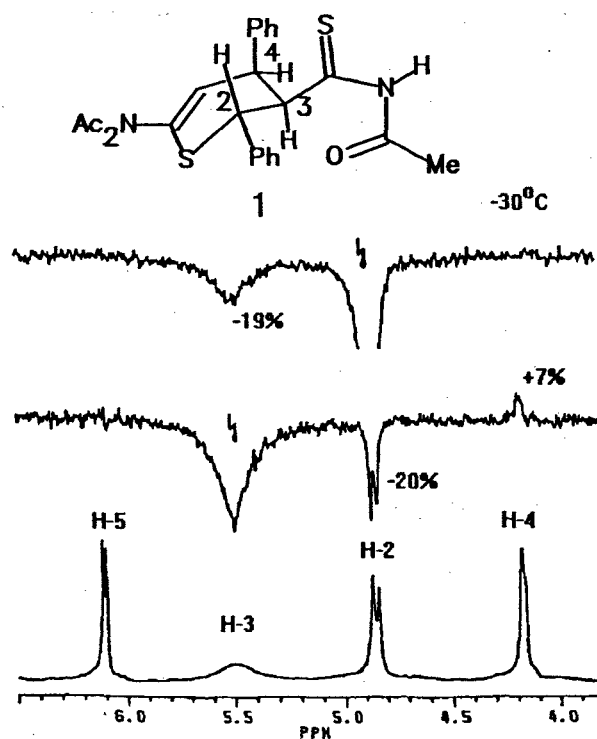

Figure 4. A segment of the NOE difference spectra showing negative peaks in the case of **1**. (CDCl₃, -30 °C, 400 MHz).

The mystery:

During these invetigations a highly unusual phenomenon was observed in the $^1H\{^1H\}$ NOE difference spectra of compounds **1** and **2**, in that the H-3 and H-2 protons are connected by massive negative peaks while all other NOEs are positive as illustrated in Figs. 3 and 4.

The facts:

a) The observed effect involves H-2 and H-3 only.

b) The phenomenon appears to be specifically linked to the presence of the $C=O$ unit in the sidechain, and is compeletely absent in **3** and **4**.

c) As measured at 400 and 300 MHz, respectively, the negative peaks showed no field dependence beyond that attributable to experimental errors.

d) The intensity of the negative enhancements increases markedly with decreasing temperature and viscosity, and tends towards zero at elevated temperatures in accordance with the antiperiplanar arrangement of H-2 and H-3:

Negative enhancements at 400 MHz, measured at various temperatures using otherwise identical experimental parameters:

	CDCl3			DMSO
1	-30°C	+25°C	+50°C	+25°C
	-20%	-3%	0%	-14%
2		+25°C	+50°C	
		-14%	-4%	

e) The nonselective T_1 relaxation times of all ring protons in **1** (CDCl3, +25°C, 400 MHz) were measured to be ca. 1 s. This accords with the size and expectedly fast tumbling of the molecule.

Conceivable (but rejectable) explanations:

The effect seems to be inexplicable in terms of the well understood cross-relaxation or conceivable saturation transfer processes:

a) The trivial case of irradiation spillover can be discounted because: 1) This would be incompatible with the observed temperature dependence of the negative peaks; 2) Fig. 4. illustrates a situation in which the signal due to H-3 is "halfway" in between those of H-5 and H-2, of which only the latter shows the negative effect. (The irradiation power levels used in all experiments were: 54L (Bruker AM 400) and DLP=30 (Varian VXR-300).

b) A three-spin effect is geometrically unjustified, and is incommensurate with the magnitude of these negative enhancements.

c) The possibility of saturation transfer may be considered as being the result of some form of chemical exchange in **1** and **2**. Possible options are: 1) direct proton transfer between H-2 and H-3. However, ^1H and ^2H NMR studies on the C(3)-^2H labeled isotopomer of **1** have conclusively shown that any possibility of a stereoselective H-2--H-3 proton transfer can be discounted. 2) A possible chemical exchange may also involve restricted ring pseudorotation or restricted C(3) sidechain mobility, both being slow on the chemical shift time-scale. Assuming that in such a hypothetical situation the H-3 signal of the minor conformer lies directly underneath the H-2 signal of the major conformer (and vice versa !), this could lead to negative peaks that are (vaguely) similar to those observed in the NOE difference spectra. However, such a situation can be ruled out on account of several quite obvious considerations, the most trivial being that 1) the multiplet patterns of the observed negative peaks do not conform to those expected for either of the above possibilities for slowly interconverting conformational species; 2) the phenomenon is observed only in relation to H-2 and H-3.

Moreover, the observed temperature and viscosity dependence of the effect is contrary to that normally expected for saturation transfer: 1) The longer correlation times associated with higher solution viscosity (in our case in DMSO) or lower temperatures are, in the extreme narrowing limit, related to more efficient T_1 relaxation which works against saturation transfer. 2) Decreased temperatures usually diminish the efficiency of the exchange process.

d) A major contribution from scalar relaxation [3] which could be perceived as being brought about by the somewhat labile character of H-3 can be ruled out since the J(H-2,H-3) couplings show no sign of the rapid modulation that would result in the collapse of the relevant multiplet patterns.

e) Strong coupling effects [4] are not present, and would not give negative peaks of this size.

f) Anisotropic reorientation in the intermediate region between fast and slow tumbling can be considered. This carries the possibility of exhibiting small positive and small negative enhancements simultaneously. However, all the positive enhancements measured between spatially analogously related protons in **1-4** were of similar magnitude, and in line with that expected for a fastly tumbling molecule.

The phenomenon therefore still awaits adequate rationalization. The question of how the effect may be related to the geometrical and constitutional specifics of these molecules is still being pursued.

References:
1. I.T. Barnish, C.W.G. Fishwick, D.R. Hill, Cs. Szántay Jr., *Tetrahedron,* **45** (1989) 6771.
2. Cs. Szántay Jr., I. Moldvai, C.W.G. Fishwick, D.R. Hill, *Tetrahedron Lett.,* **32** (1991) 2529.
3. D. Neuhaus, M.P. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis,* VCH Publishers, New York, 1989, pp. 203-207.
4. J. Keeler, D. Neuhaus, M.P. Williamson, *J. Magn. Reson.,* **73** (1987) 45.