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STEREOCHEMICAL ELUCIDATION OF ISOMERIC TRICYCLIC 1,4-BENZODIOXANS (II)[1]
BY THE USE OF THE NMR SHIFT REAGENT, $Eu(fod)_3$

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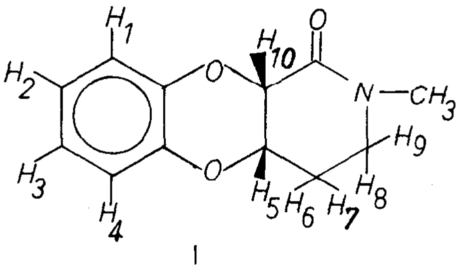
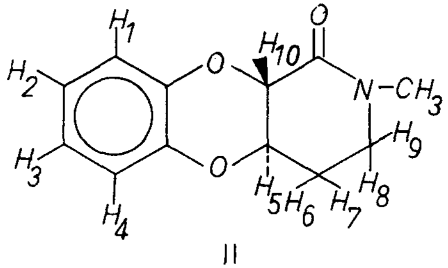
Recently the use of two new shift reagents, $Eu(fod)_3$ and $Pr(fod)_3$, have been reported by Rondeau and Sievers.[2] The advantage of these as shift reagents is due to their relatively high solubility in nonalcholic solvents and to the fact that neither $Eu(fod)_3$ nor $Pr(fod)_3$ contribute to peak broadening.[2]

In a research program leading to the development of potentially useful medicinal tricyclic benzodioxans, the cis(I)- and trans(II)-isomers were prepared.[1]



I



II

In order to differentiate between I and II $Eu(fod)_3$ was used to shift the peaks so that the coupling constants for the ring fusion protons could be measured. The coupling constants together with relative shifts for various protons in I and II allow the stereochemistry to be assigned.[3,4,5,6] It can be seen from shifted spectra (A and C of Fig. 1) that the fusion protons have been clearly shifted from each other. On the other hand, overlap of the fusion

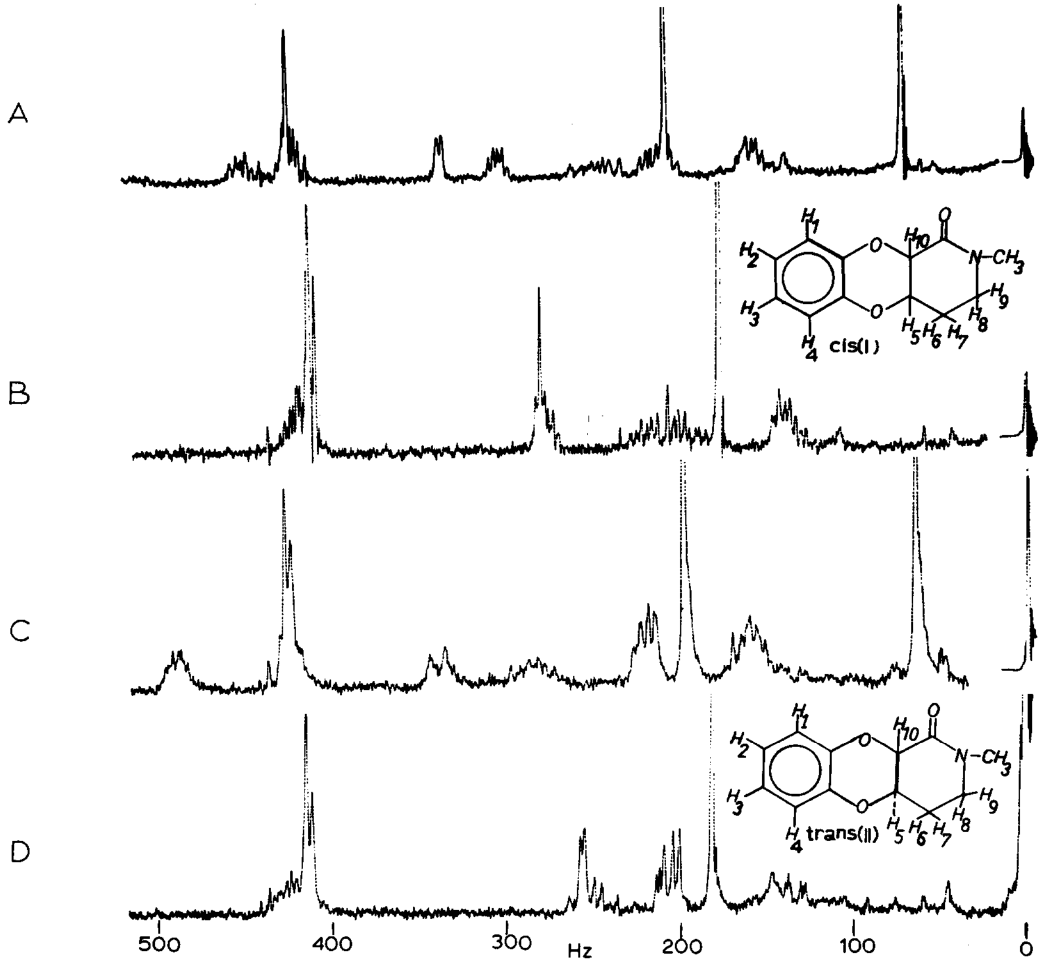


Figure 1. 60 MHz Spectra of cis- and trans-tricyclic benzodioxans.

A: Spectrum of I plus Eu(fod)$_3$ in CDCl$_3$ (9.4 x 10^{-3} moles Eu(fod)$_3$/cis I)

B: Spectrum of I in CDCl$_3$ (8.8 x 10^{-5} moles cis)

C: Spectrum of II plus Eu(fod)$_3$ in CDCl$_3$ (7.2 x 10^{-2} moles Eu(fod)$_3$:trans II)

D: Spectrum of II in CDCl$_3$ (7.25 x 10^{-5} moles trans)

The proton assignment was based on decoupling at 60 MHz.

Table I. Chemical and Paramagnetic Shifts with Eu(fod)$_3$

	Proton	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	NCH_3	mole ratio Eu(fod)$_3$: I and II
I													
Chemical shifts*	(Hz)	420	410	410	410	280†	138	138	206	206	280	177	
Paramagnetic shifts	(Hz)	825	546	575	575	537	320	320	475	475	694	451	1.1
II													
Chemical shifts*	(Hz)	430	413	413	413	256†	140	140	206	206	256†	181	
Paramagnetic shifts	(Hz)	1100	543	510	510	573	308	308	360	360	1008	143	1.2

*Downfield from internal TMS.

†Shift values only approximate due to overlap.

protons in the unshifted spectra (B and D of Fig. 1) makes a clear stereochemical assignment impossible. In the trans-isomer the coupling constant for the fusion protons, $J_{5,10}$, is 9.5 Hz. For the cis-isomer, $J_{5,10}$ is 3 Hz at low mole ratios (<0.48) of Eu(fod)$_3$ to cis-isomer. At high mole ratios (>0.48), however, $J_{5,10}$ is 8 Hz. That the trans-isomer does not show any change in the coupling constant for the fusion protons is in good agreement with the rigidity one would associate with the trans-isomer.

The maximum chemical shifts obtained with I and II are shown in Table I. It is of interest to note that H_1 shifts a great deal more downfield in the trans-isomer than it does in the cis-isomer. It should also be noted that the NCH_3 in the trans-isomer shifts much less than it does in the cis-isomer while H_{10} in the trans-isomer shifts much more in the cis-isomer. This data is consistent with the predictions based on Dreiding models.

In the cis-isomer the change in the coupling constant appears to be the result of two sets of competing equilibria, the conformational equilibria and the exchange equilibria between Eu(fod)$_3$ and the cis-isomer. At high Eu(fod)$_3$ mole ratios conformational changes in the cis-isomer become slow with respect to the exchange rate and thus a particular conformer is favored over all others.[7] It is apparent that care must be exercised in assigning stereochemistry on the basis of coupling constants alone when shift reagents are employed in obtaining them.

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7. Several equilibrating conformations of the cis-isomer may actually exist in the complex with Eu(fod)$_3$. In any case, the large value of $J_{5,10}$ indicates a dihedral angle approaching 0° for the cis-isomer at high Eu(fod)$_3$ mole fractions.