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DETERMINATION OF THE STEREOCHEMICAL CONFIGURATION OF 3-SUBSTITUTED N,N-DIMETHYL-5H-DIBENZO-[a,d]CYCLOHEPTENE-$\Delta^{5,7}$-PROPYLAMINE DERIVATIVES USING TRIS-(DIPIVALOMETHANATO)-EUROPIUM AS A SHIFT REAGENT

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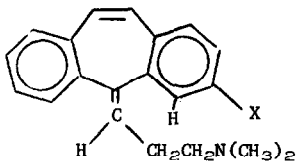
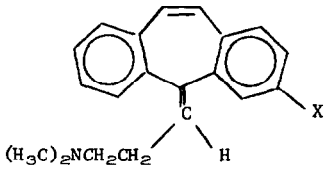
Nuclear magnetic resonance spectroscopy (NMR) has been used to determine the stereochemical homogeneity of unsymmetrically substituted dibenzocycloheptene derivatives. 3-Chloro-N,N-dimethyl-5H-dibenzo[a,d]cycloheptene-$\Delta^{5,7}$-propylamine (3-chlorocyclobenzaprine) was prepared and separated into the Z[1] (cis, 1, β-form, m.p. of hydrogen maleate salt: 156-158° (uncorr.); reported[2]: 157-158°) and E (trans, 2, α-form, m.p. of hydrochloride salt: 230.5-234.5° (uncorr.); reported: 229.5-230.5°[2], 227-229°[3]) geometric isomers by fractional crystallization. X-ray crystallography has established that the β-form has the Z configuration[4].



Z

1. X = Cl

4. X = $-SO_2CH_3$



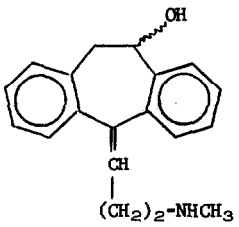
E

2. X = Cl

5. X = $-SO_2CH_3$

Examination of the NMR spectra of the free bases 1 and 2 in CS_2 shows that the N-methyl protons of the Z isomer, 1, absorb as a singlet (δ2.4-2.5) between 2-3 Hz downfield from the N-methyl protons of the E isomer, 2. Thus, the progress of preparing stereochemically pure 1 and 2 during fractional crystallization of their salts, as well as the homogeneity of the final samples, can be determined by NMR spectroscopy.

This method has also been used during the preparation and separation of the E and Z isomers of 10-hydroxynortriptyline (3). These compounds were prepared as reference samples for a study of the metabolites of amitriptyline[5,6].



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In an attempt to enhance the difference in chemical shifts of the N-methyl protons in 1 and 2, the NMR spectra of these isomers were re-examined in the presence of the recently reported[7] tris-(dipivalomethanato)europium, $Eu(DPM)_3$. As expected, the addition of the europium complex to solutions of 1 and 2 resulted in a downfield shift of those protons close to the complexing site, the basic nitrogen atom. Table I gives the chemical shifts of the N-methyl protons of 1 and 2 induced by different concentrations of $Eu(DPM)_3$, and the differences between these chemical shifts. At the lowest concentration of $Eu(DPM)_3$ studied, the Z isomer, 1 showed a greater chemical shift for these protons than did the E isomer, 2. At the highest concentration of $Eu(DPM)_3$ studied, the E isomer, 2, showed a greater shift for these N-methyl protons than did the Z isomer, 1. Thus, in the latter case, an approximate 12-fold increase in the separation of the resonances of the N-methyl protons of 1 and 2 has been realized between the europium complexed isomers and their non-complexed counterparts. This improved definition allows for a better assessment of the stereochemical homogeneity of the isomer samples.

For both 1 and 2, the main aromatic envelope in the europium complexed spectra occurs at δ7.0 to δ8.0. The aromatic proton at position 4 in the Z isomer, 1, however, experiences a downfield shift, presumably due to the close proximity of this proton to the europium-amine complexing site. Indeed, the proton at position 4 in the Z isomer, 1, is shifted from under the aromatic envelope to δ8.87 ($Eu(DPM)_3$ 0.443M), δ9.73 ($Eu(DPM)_3$ 0.665M) and δ10.37 ($Eu(DPM)_3$ 0.882M), while the proton at position 4 in the E isomer, 2, experienced no comparable shift. In each of the un-complexed isomers this proton resonance is within the aromatic envelope. A comparison of the spectra of 1 and 2 in the presence of the shift reagent $Eu(DPM)_3$ therefore provides a method for assignment of stereochemical configuration between 1 and 2.

The NMR spectra of the two pure geometric isomers of 3-methylsulfonylcyclobenzaprine[8] (Z, 4, cis, β-form; and E, 5, trans, α-form) in the presence of $Eu(DPM)_3$, 0.502 mole per mole

TABLE I

NMR SPECTRA OF E AND Z 3-CHLOROCYCLOBENZAPRINES: SHIFTS OF THE N-METHYL PROTONS INDUCED BY $Eu(DPM)_3$ [a]

COMPOUND (STEREOCHEMISTRY)	MOLES OF $Eu(DPM)_3$ PER MOLE SUBSTRATE [b]	δ $N(CH_3)_2$	$\lvert\Delta\delta\rvert$ $\lvert\delta_Z-\delta_E\rvert$
1 (Z)	0.443	12.63	0.30
2 (E)	0.443	12.33	
1 + 2 [c]	0.443	12.65, 11.43	1.22
1 (Z)	0.665	18.18	0.21
2 (E)	0.665	17.97	
1 + 2 [c]	0.665	18.13, 16.73	1.40
1 (Z)	0.882	22.17	0.60
2 (E)	0.882	22.77	
1 + 2 [c]	0.882	21.40, 22.57	1.17

(a) "Eu-Resolve", Ventron Corporation.

(b) Solutions were prepared by mixing 50.0 mg. of 1 or 2 with the appropriate weight of $Eu(DPM)_3$ in 0.5 ml. of CCl_4, allowing them to stand for 24 hours, then filtering the slightly turbid solutions. The spectra were measured on a Varian A-60A and all shifts are relative to tetramethylsilane as an internal standard.

(c) Equal volumes of the solutions of 1 and 2 of similar $Eu(DPM)_3$ concentration were mixed.

of substrate, were also examined. In this case, the N-methyl protons of 4 were shifted to δ11.47, while those of the E isomer, 5, were shifted to δ13.67 ($|\Delta\delta$2.20$|$).

For both 4 and 5, the main aromatic envelope in the europium complexed spectra occurs at δ7.0 to δ8.0. The aromatic proton at position 4 in the Z isomer, 4, however, experiences a downfield shift and resonates at δ10.78. A comparable shift is not observed with the E isomer, 5. In each of the un-complexed isomers, this proton resonance is within the main aromatic envelope (δ6.8 to δ8.0).

The protons of the methyl groups in the 3-methylsulfonyl moieties of 4 and 5 also experience a downfield shift in these europium complexed spectra. Thus, the protons of the 3-

methylsulfonyl group of the Z-isomer, 4, were shifted to δ4.70, while these protons in the E isomer, 5, were shifted to δ3.87. In the uncomplexed spectra of 4 and 5, the protons of the 3-methylsulfonyl groups both appeared at δ3.03 ($CDCl_3$).

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