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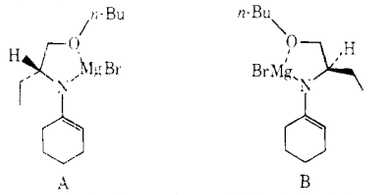
(7) Subsequent to the initial submission of this manuscript, an article describing quite similar results appeared [A. I. Meyers, D. R. Williams, and M. Druelinger, *J. Am. Chem. Soc.*, **98**, 3032 (1976)]. The rationale offered by these authors to explain both the degree and direction of their asymmetric induction could be used to explain our results as well. We are bothered, however, by the incorporation of three collinear atoms within a six-membered transition state that is necessitated by their explanation for alkylation by alkyl halides (assuming a trigonal bipyramidal arrangement about the alkylating carbon atom). We offer the following, alternative rationale. Assuming that there is *lone-pair–π*-system overlap in the transition state, then there are two conformations relative to the developing nitrogen–carbon π bond, and while the chiral center is remote from the atom undergoing alkylation in conformation A, it is quite proximate in B. A similar situation obtains during the



A B

alkylation of proline derived enamines which yield, at best, 43% enantiomeric excess of alkylcyclohexanone.[8] In the present case, however, the magnesium atom would be expected to be aggregated and/or highly solvated, thus providing a possibly serious steric inhibition to alkylation via conformation A that would not be apparent in the proline derived enamines. A high degree of enantioselectivity would thus be expected if alkylation occurs mainly or exclusively via B, where the ethyl substitutent is well situated to direct alkylation to the side of the molecule corresponding to the *R* configuration actually obtained.
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Stereoisomerism of Cyproheptadine *N*-Oxide

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The synthesis of cyproheptadine *N*-oxide (**1**) has been described in the patent literature.[1] Subsequent studies of the metabolic fate[2] of cyproheptadine necessitated the resynthesis of **1**. The findings that the hydrogen peroxide oxidation of cyproheptadine provided two isomeric *N*-oxides in the approximate ratio of 75α:25β, and that the α isomer was a major metabolite in the dog, prompted us to investigate the stereochemistry of these isomers.

The isomers were distinguishable by TLC and separable by column chromatography. Their interconversion was evidenced by the precipitation of the β isomer from a refluxing toluene solution of the α isomer. They showed clear differences in their ^{1}H NMR spectra, markedly so in the position of the N-CH_3 singlet which appeared for the β isomer at 0.16 ppm downfield from that of the α isomer (Table I). This distinction was useful for determination of the isomeric purity of the two compounds. The piperidine ring methylene groups, which showed distinct differences in chemical shift in the two isomers, were of little diagnostic value owing to overlapping signals.

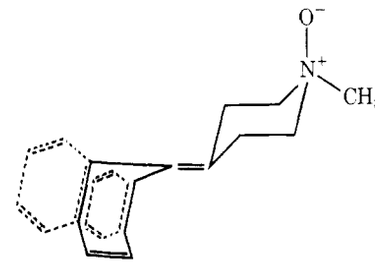
The ^{13}C NMR spectra of the two isomers provided evidence that the N-CH_3 group has the same orientation in both compounds since the chemical shift for the N-CH_3 group appeared at ca. 56 ppm in both isomers. These spectra were determined for the hydrochloride salts of the two isomers. In the ^{13}C NMR spectrum of the quaternary salt, 1,1,4-trimethylpiperidinium iodide, the chemical shift of the equatorial N-CH_3 group is 56.0 ppm and that of the axial N-CH_3 group is 47.8 ppm.[3] Thus, an equatorial N-CH_3 group is suggested for both isomers of the *N*-oxide. This conclusion is supported by a reported[4] ^{1}H NMR study on 1-methylpiperidine 1-oxide which indicated that this potentially mobile *N*-oxide exists preferentially as the conformer with the N^+–O^- bond axial. Other work also has provided evidence that an axial orientation for N-oxidations is preferred.[3,5]

Table I. NMR Assignments of Cyproheptadine *N*-Oxides

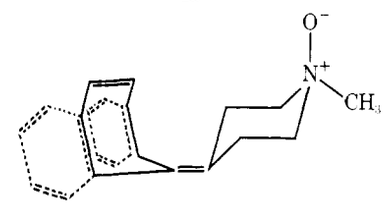
Isomer	δ_{1_H} (N-CH_3)[a]	δ_{1_H} (C_{10} + C_{11})[a]	δ_{13_C} (N-CH_3)[b]
α	3.12	6.88	56.2
β	3.28	6.88	56.0
α + LSR[c]		6.96[d]	
		7.02[e]	
β + LSR[c]		6.84[f]	
		6.78[g]	

[a] Determined for the base in $CDCl_3$, Me_4Si internal standard. [b] Determined for the hydrochloride salt in Me_2SO-d_6, Me_4Si internal standard. [c] LSR = Eu(hfbc)$_3$. [d] 4 mg of LSR added to 5 mg of base/0.5 ml of $CDCl_3$. [e] 8 mg of LSR added to 5 mg of base/0.5 ml of $CDCl_3$. [f] 4 mg of LSR added to 4.6 mg of base/0.5 ml of $CDCl_3$. [g] 6.7 mg of LSR added to 4.6 mg of base/0.5 ml of $CDCl_3$.

Construction of Dreiding models of the cyproheptadine *N*-oxides in conjunction with these data indicated that the two compounds in hand were the isomers **1a** and **1b**, differing only



1a



1b

in the conformation of the dibenzocycloheptene ring. However, the observed spectral characteristics did not permit stereochemical assignments to be made. Further ^{1}H NMR studies employing a lanthanide shift reagent (LSR) provided a basis for assigning the stereochemical relationship between the N^+–O^- bond and the aromatic ring system in the two *N*-oxides. A difference in the location of the C_{10} and C_{11} protons relative to the lanthanide–oxygen–nitrogen grouping is indicated by the fact that these protons in the two isomers are displaced in opposite directions upon addition of the LSR (Table I). The upfield shift of the C_{10} and C_{11} protons in the β isomer implies that these protons are syn with respect to the N^+–O^- bond. This relationship follows from the 3 $\cos^2\theta - 1$ term of the McConnell–Robertson equation[6] which governs the direction in which a nearby proton is displaced. The angle θ is defined by the donor atom, the lanthanide, and the proton under consideration. The expression changes sign at ca. 50°

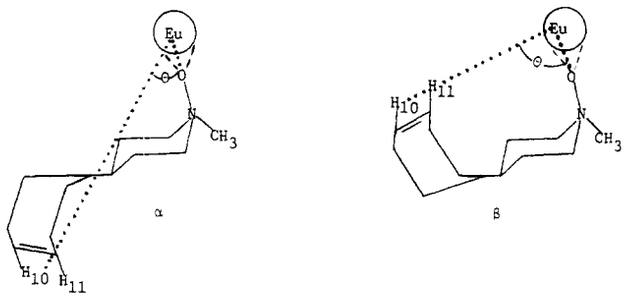


Figure 1. Stereochemical relationship between the N^+–O^- bond and the ethylene bridge protons in the europium complexed $\alpha + \beta$ isomers of cyproheptadine *N*-oxide.

so that a proton associated with a θ value greater than 50°, e.g., the β-C_{10} proton, would experience an upfield shift. These stereochemical relationships then may be represented diagrammatically for the two isomers as in Figure 1 and the α isomer assigned structure **1a**, the β isomer, structure **1b**.

Confirmation of these assignments was sought from calculations of the theoretical values for the $3(\cos^2\theta - 1)/r^3$ term for varied conformations of the isomeric europium complexes.[7] Because of the observed equivalence of H-10 and H-11, the europium atom must be positioned either (a) in a single conformation which is symmetrical with respect to the C_{10}–C_{11} double bond or (b) in two or more rapidly interconverting conformations such that on the average H-10 and H-11 are equivalent. For situation a, only two Eu–O–N–CH_3 dihedral angles, 0 and 180°, are acceptable. The calculations indicated that as long as the Eu–O–N angle was greater than 150°, the predicted direction for the lanthanide-induced shifts was as observed experimentally. In fact, owing to steric hindrance, no Eu–O–N dihedral angle of less than 150° would be expected. For situation b, the two most reasonable conformations are the staggered ones with Eu–O–N–CH_3 dihedral angles of 60 and 300°. In this case, the calculations indicated that the predicted direction of the shifts matched the experimental observations, provided the Eu–O–N angle exceeded 120°. Here also, no smaller Eu–O–N angle would be expected on either electronic or steric grounds.

Thus, the stereochemical relationships for the complexed isomers represented in Figure 1 appear valid and structure **1a** may be assigned to the α isomer and **1b** to the β isomer of cyproheptadine *N*-oxide.

Experimental Section[8]

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine 1-Oxide (1a and 1b). A stirred solution of cyproheptadine (14.8 g, 0.0515 mol) in 150 ml of MeOH was treated portionwise with 30% H_2O_2 (18 g) and then held at room temperature for about 10 days. The cooled solution was stirred with a suspension of ca. 200 mg of 5% Pt/C in 1 ml of H_2O until the excess peroxide was destroyed. Evaporation of the filtered solution at 35 °C left a solid residue that was dried overnight at 20 mm over P_2O_5. The solid then was pulverized and dried at 0.2 mm over P_2O_5 for 24 h; yield, 15 g of the mixture of isomers.

A 10-g sample of the product was chromatographed on 700 g of SiO_2, eluting with 15 MeOH–85 $CHCl_3$. Fractions containing a single component of R_f 0.5 by TLC (20 MeOH–80 $CHCl_3$ development) were combined to afford the solvated crystalline α base **1a**. This was recrystallized from H_2O to give 5.2 g of the crystalline hemihydrate, mp 188–191 °C, after prolonged drying at room temperature at 0.2 mm.

The α-hydrochloride hemihydrate precipitated from a solution of the base in EtOH–HCl(g) and was recrystallized from EtOH, mp 205–211 °C dec.

Chromatographic fractions containing a single component of R_f 0.4 by TLC were combined to afford the crystalline β base **1b**, mp 194–199 °C dec. This base was not readily recrystallized and was converted to the hydrochloride salt with EtOH–HCl(g). The salt was recrystallized from EtOH to give 1.9 g, mp 223–228 °C dec, after prolonged drying at room temperature at 0.1 mm.

Isomeric purity of the hydrochloride salts was determined to be >95% by both NMR and TLC (10 benzene–80 dioxane–10 concentrated NH_4OH development).

A solution of the α base **1a** (6.0 g, 0.02 mol) in 175 ml of toluene was stirred at reflux for 24 h. After 2 h, a white solid had begun to precipitate. The solid was collected from the cooled mixture by filtration and triturated with hot toluene (50 ml). The remaining solid (4.3 g) was dissolved in EtOH–HCl(g). The hydrochloride salt precipitated and was recrystallized from EtOH to give 4.1 g, mp 228–231 °C dec. This material was identical in all respects with the hydrochloride of the β isomer **1b**.

Acknowledgment. The authors wish to thank Dr. Laurance D. Hall of the University of British Columbia, Vancouver, Canada, for valuable advice and discussion, as well as for the calculations of the configurations of the lanthanide complexes.

Registry No.—**1a,** 54381-42-9; **1a** HCl, 60304-94-1; **1b,** 60251-34-5; **1b** HCl, 60268-34-0; cyproheptadine, 129-03-3.

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(7) These calculations were carried out by Victoria C. Gibb, using a computer program developed in the laboratory of Dr. Laurance D. Hall at the University of British Columbia, Vancouver, Canada. Standard values for all bond lengths and angles were used. Values for $\theta_{O,Eu,H}$ and $r_{Eu,H}$ were measured from Dreiding models, assuming no rotation of the europium atom around the N–O bond and the same relative position and binding constant of the metal for both isomers. Variations in the isomeric binding constants would effect only the magnitude but not the direction of the induced shifts.
(8) Melting points were determined with a calibrated thermometer in a Thomas-Hoover apparatus. ^1H NMR spectra were recorded on a Varian HA-100D spectrometer; ^{13}C NMR on a Varian CFT-20. Thin layer chromatography was done on precoated silica gel plates with UV indicator supplied by Analtech, Inc. Evaporations were carried out in a rotary evaporator at reduced pressure. Satisfactory analytical data (±0.4% for C, H, N) for **1a** and **1b** were submitted for review.

A Convenient Synthesis of Diaryl Methylphosphonates and Transesterification Products Therefrom

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Diaryl methylphosphonates have been useful as both enzyme model substrates[1] and reactive intermediates.[2] The literature describes two basic routes for their preparation. One involves the condensation of methylphosphonic dichloride with the appropriately substituted phenol.[3] However, methylphosphonic dichloride is not readily available and low yields have been reported in some of the aryl ester syntheses using this reagent. The second procedure[4] consists of reacting a triaryl phosphite with 1 equiv of methyl iodide. This Michaelis–Arbuzov rearrangement gives only modest yields, for instance, less than 70% in the case of 1. Moreover, it requires methyl iodide, an expensive reagent. We report, herein, an improved version of the latter rearrangement.

Our procedure involves addition of 1 molar equiv of methanol containing a catalytic amount of methyl iodide to a triaryl phosphite at 200–250 °C. The reaction, on a five molar scale,