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^{1}H NMR spectral simplification with achiral and chiral lanthanide shift reagents — IV.* Thiopental and barbiturate analogues

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Abstract: The 60 MHz ^{1}H NMR spectra of racemic thiopental, **1**, have been studied with the achiral shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium(III), **2**, and the chiral tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), **3**, and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III), **4**. Enantiomeric shift differences, $\Delta\Delta\delta$, were clearly observed for all three methyl signals of **1** with **3** or **4**, with larger values obtained using the former reagent. Thus, a 0.216 molal solution of **1** in $CDCl_3$ at 28°C with a **3**:**1** molar ratio of 0.359 displayed $\Delta\Delta\delta$ values of about 17 Hz for the proximal methyl of the methylbutyl group (at the chiral centre), 13 Hz for the CH_3 of the ethyl group, and 6 Hz for the distal CH_3 of the methylbutyl group. Results are compared for those obtained with **2** and **3** using secobarbital, talbutal, butabarbital and pentobarbital.

Keywords: *Thiopental; barbiturates; optical purity determination; lanthanide shift reagents.*

Introduction

Configurations of chiral centres in molecules have great importance. Recently, some high-performance liquid chromatographic (HPLC) methods have shown much promise for enantiomer separation and optical purity determinations. However, some workers have suggested that certain important classes of drugs may not be amenable to these techniques [1]. One such class was that of barbiturates in which the chiral centre was not part of the pyrimidinetrione ring.

Lanthanide shift reagents (LSR) have proven exceedingly useful since their introduction [2] for NMR spectral simplification. The subject has been reviewed [3–11]. Chiral LSRs have been valuable for direct optical purity determinations [12]. Often, the abundant structural data provided by NMR has much value well beyond the limited retention time information provided by simpler HPLC detectors commonly in use. For

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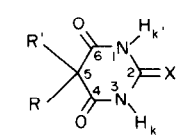
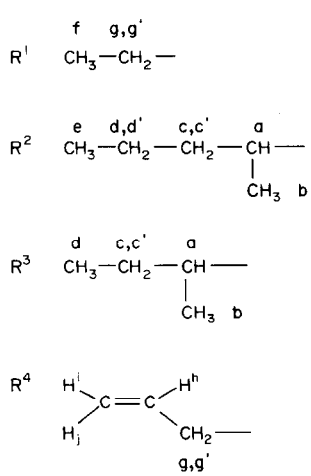
the particular example of barbiturates, cited above, the chiral LSR method has been shown to be successful in thiohexital [13] and thiamylal [14], sulphur analogues of barbiturates in which the sole chiral centre lies outside the heterocyclic ring. The authors strongly feel that the two methods of chiral HPLC and chiral LSRs will both continue to prove to be very valuable and complementary analytical techniques.

Since significant differences in potency were observed for the optical antipodes of the barbiturate, methohexital [15], the stereochemistry of barbiturates and analogues has been of interest. The chiral LSR method has been reported for methohexital [16], hexobarbital [17] and mephobarbital [18]. The enantiomers of a number of barbiturates and analogues have been synthesized and studied [19–29]. For thiopental, the *S*(−) isomer was found to have significantly more acute toxicity and anaesthetic activity than the *R*(+) isomer or the racemate, based on studies in mice; corresponding relative potencies were also found to be greater for the *S*(−) isomers of pentobarbital, secobarbital and thiamylal [25]. We report here the results of studies with thiopental, **1**, dihydro-5-ethyl-5-(1-methylbutyl)-2-thioxo-4,6(1H,5H)-pyrimidinedione, also known as 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid, and commonly used as a short-acting intravenous anesthetic. ^{1}H NMR studies were performed with the achiral shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III), **2**, abbreviated as Eu(FOD)$_3$, and the chiral shift reagents tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), **3**, known as Eu(FACAM)$_3$ or Eu(TFC)$_3$, and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), **4**, known as Eu(HFC)$_3$ or Eu(HFBC)$_3$. In addition, comparative data are presented for runs with **2** and **3** using barbiturate substrates which include pentobarbital (**5**), butabarbital (**6**), secobarbital (**7**) and talbutal (**8**).





1: R = R^1, R' = R^2, X = S
5: R = R^1, R' = R^2, X = O
6: R = R^1, R' = R^3, X = O
7: R = R^4, R' = R^2, X = O
8: R = R^4, R' = R^3, X = O
9: R = R^4, R' = R^2, X = S

Experimental

A sample of racemic thiopental (batch B123-4) was kindly provided as the free acid by May and Baker Ltd., Dagenham Essex RM10 7XS (England), and was used as received. The sample had mp (uncorrected) 156.0–158.0°C; lit. 158–159°C [30], 157.5–159°C [31], 156–157°C [32]. Chloroform-*d*, (99.8 at.% D), obtained from Aldrich Chemical Co., Milwaukee WI 53201 or from Norell Inc., Landisville NJ 08326, was dried and stored over 3A molecular sieves. Shift reagents were obtained from Aldrich and were stored in a desiccator over P_2O_5. Materials were used as supplied except as noted.

In general, an accurately weighed portion of drug (about 20–40 mg) was added to about 600 mg of $CDCl_3$ (containing about 0.2% tetramethylsilane (TMS) as internal standard) in an NMR sample tube and dissolved by shaking; increments of shift reagent were added, dissolved by shaking, and the spectra immediately run.

All spectra were run on a Varian EM-360A 60 MHz ^{1}H NMR spectrometer at a probe temperature of 28°C. Chemical shifts are reported in parts per million (δ) relative to TMS as internal standard and are believed accurate to ±0.05 ppm. In spectra where TMS was obscured by shift reagent peaks, $CHCl_3$ (present as an impurity in the solvent) was used as the internal standard.

Analogous techniques were used for the other substrates reported here.

Results and Discussion

Thiopental, **1**, is the 2-thio analogue of pentobarbital, **5**. In butabarbital, **6**, the 1-methylbutyl group of **5** has been replaced by the smaller 1-methylpropyl group. Secobarbital, **7**, is the 2-oxo analogue of the thiamylal, **9**, a thiobarbiturate reported earlier [14]. Both **7** and talbutal, **8**, are barbiturates in which the 5-ethyl substituents of **1**, **5** and **6** are replaced by allyl groups. Where **1**, **5** and **7** have a 1-methylbutyl substituent at the C_5 position of the ring, **8** (like **6**) has the smaller 1-methylpropyl group. All of these compounds possess a single chiral centre external to the heterocyclic ring. The present results now permit direct comparisons of two pairs of oxobarbiturate–thiobarbiturate analogues, **1** with **5**, and **7** with thiamylal, **9**. Comparisons between **5**–**8** show effects of varied substituents at the ring C_5 position. Previous reports for thiohexital and thiamylal, together with present results for thiopental, suggest that the chiral LSR technique is readily applicable to 2-thiobarbiturates in which the sole chiral centre lies outside the ring. The only 2-oxobarbiturates which have previously been found to be amenable to chiral LSR methods for direct optical purity analysis, e.g. methohexital, hexobarbital and mephobarbital, have each had a chiral centre as part of the pyrimidinetrione ring, at C_5.

^{1}H NMR spectra for thiopental, pentobarbital, butabarbital, talbutal and other barbiturates have been published using dimethyl sulfoxide-d_6 as solvent [33], along with spectral data for **1**, **5**, **6** and **7** as Na salts in the same solvent. ^{13}C NMR has also been applied to barbiturates, including sodium secobarbital in mixtures [34]; **1**, **5**, **6**, **7** and others (as free acids or Na salts, in different solvents) [35]; **5** and others [36, 37]. Other extensive discussions of ^{13}C NMR of barbiturates have also appeared [38].

Precise chemical shift assignments for the substrates examined here are rendered difficult because of severe overlaps, particularly in absorptions in the high field region. An NMR spectrometer operating at higher frequencies would prove extremely useful, since the resulting improved dispersion would not only simplify spectral assignments but

would also facilitate applications for optical purity determination. The significance of the present findings is seen to lie in the demonstration of major differences between thiobarbiturates and oxobarbiturates and in the demonstration of the feasibility of direct optical purity determinations using chiral LSRs for the former compounds. The authors' assignments for those proton signals in severely overlapped regions are believed correct within ±0.1 ppm. Generally, moderate additions of shift reagents allow signal separations that permit shift assignments to ±0.05 ppm.

Thus, the authors have assigned signals in the unshifted reference spectrum of **1** as a 0.164 molal solution in $CDCl_3$ at 28°C as follows, in δ (ppm): 9.42 (broad s, 2H, NH); 2.13 (approximate *q* superimposed on broad mult, 3H, $H_{g,g'}$ and H_a); 1.30 (complex mult, 2H, $H_{c,c'}$). The complex region from *ca* 0.8–1.3 δ was assigned as: 1.10 (mult, 2H, $H_{d,d'}$); 1.03 (d, 3H, H_b); 1.00 (t, 3H, H_f); 0.93 (t, 3H, H_e) with four distinct peaks of the overlapping methyl signals being discernible. Assignments in these regions were assisted by extrapolation to zero LSR levels from plots of δ versus [LSR]:[substrate] derived from spectra with added shift reagent. This method was also used for assignments of the other barbiturates.

With additions of $Eu(FOD)_3$, the spectra of **1** were greatly simplified. The most striking changes were the clean separations achieved for the three methyls which were part of the complex upfield multiplet in the unshifted reference spectrum. At **2:1** molar ratios near 0.22, the doublet for the H_b methyl had moved downfield completely past the triplet H_f methyl. The Δδ values were distinctly greater for the more hindered H_b although both methyls are separated from the expected carbonyl complexation sites for europium by the same number of bonds. This could suggest that a preferred conformation of the 1-methylbutyl substituent in **1** bound to lanthanide places H_b closer to the metal; angular factors may also contribute to the relative Δδ values. The distal methyl, H_e, displays small Δδ values as expected by its location far from the basic sites, and is initially obscured by overlap with resonances of **2**. At a **2:1** ratio of 0.84, it has moved downfield just clear of the shift reagent signal and appears as the expected triplet. The initially overlapping signals of the methine H_a and the methylene $H_{g,g'}$ have similar lanthanide induced shifts which separate at **2:1** ratios above 0.6 into a downfield 2H intensity and an upfield 1H intensity broad multiplet. We cannot rigorously assign H_a since separation of the diastereotopic methylene signals could account for the observed patterns. Clear separation of diastereotopic methylene resonances is unambiguously seen for $H_{c,c'}$ at **2:1** ratios above 0.6, with two equal branches appearing. We could expect distinct separation for this pair of protons as more likely than for $H_{g,g'}$ since the former are closer to the chiral centre. The diastereotopic methylene protons, $H_{d,d'}$, show a signal free from overlaps at **2:1** ratios above 0.38; this broad complex multiplet did not separate into two 1H resonances at the highest **2:1** ratio used, 0.84.

In runs with the chiral $Eu(FACAM)_3$, **3**, a significant difference in relative Δδ values is observed for the diastereotopic $H_{c,c'}$ and the methyl H_b compared to results with **2**. With the achiral **2**, both absorptions of H_c and $H_{c'}$ move downfield clear of the H_b signal. With **3**, the upfield signal from the diastereotopic pair, i.e. $H_{c'}$, partly overlaps the H_b signal, interfering with potential optical purity determinations. Some evidence for overlap of $H_{c'}$ with H_f is seen with a **3:1** ratio of 1.54, the highest ratio employed. Substantial Δδ differences are also seen in the downfield regions at high LSR:**1** ratios for runs with **2** and **3**. Much greater Δδ values are seen for the NH signals with **2**.

Although severe line broadening at high LSR levels contributes to some uncertainty in assignments and ΔΔδ values, some suggestions can be made concerning recommended

conditions for optical purity analysis of **1** with **3**. Although H_b displayed $\Delta\Delta\delta$ as high as 28 Hz for a **3:1** ratio of 1.0 (which seemed to decrease slightly at a **3:1** ratio near 1.5), H_f displayed $\Delta\Delta\delta$ which continuously increased to about 30 Hz at the same LSR levels. At lower LSR levels, $\Delta\Delta\delta$ was consistently somewhat less for H_f than for H_b. Although H_b should be preferable for analytical purposes because of lower multiplicity, use of lower LSR ratios to reduce line broadening leads to overlap of $H_{c'}$ with the H_b signal. Higher LSR levels lead to the signal of $H_{c'}$ overlapping with H_f and to line broadening which raises the valley height between H_b and H_f. Even the distal methyl H_e shows very substantial $\Delta\Delta\delta$, 11 Hz at a **3:1** ratio of 0.635. The crucial point of these studies is the very high values seen for enantiomeric shift differences compared to any of the oxybarbiturate derivatives. Despite the location of the chiral centre outside the ring, $\Delta\Delta\delta$ values are large so long as the lanthanide is complexed close to the alkyl sidechains by binding to the C_4 and C_6 oxygens of the thiobarbiturate. For analytical purposes, use of lower LSR levels minimizes line broadening and gives unoverlapped signals for H_f and H_e with $\Delta\Delta\delta$ of 13 and 6 Hz, respectively, with a **3:1** ratio of 0.359.

Unexpectedly, results with $Eu(HFC)_3$, **4**, were less successful than with **3** in terms of $\Delta\delta$, $\Delta\Delta\delta$ and line broadening. The authors were unable to obtain a ratio of **4:1** that provided clean separation of peaks with adequate $\Delta\Delta\delta$ and freedom from line broadening to permit optical purity analysis up to LSR:substrate ratios of 0.8. Line broadening was more severe and $\Delta\Delta\delta$ was less with **4** relative to **3**.

The authors' results for **1** with **2**, **3** and **4** are presented in Figs 1–3, showing plots of δ versus the respective molar ratios of shift reagent to substrate. Figure 4 summarizes the variation of the enantiomeric shift differences, $\Delta\Delta\delta$, with increasing molar ratio of chiral LSR **3** or **4** to **1**. $\Delta\Delta\delta$ is defined as the magnitude of the difference in chemical shifts of a specific nucleus when chiral shift reagent is added to a mixture of the two enantiomers. It is the value of $\Delta\Delta\delta$ for a given resonance, together with lanthanide-induced peak broadening and signal overlaps, which determines the ability to use chiral LSRs for direct optical purity determinations. Comparative data for **1** and the

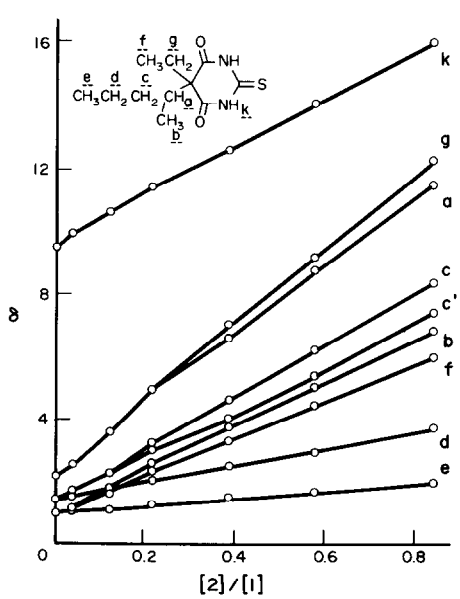


Figure 1
Variation of chemical shift, δ, with molar ratio of $Eu(FOD)_3$ to thiopental.

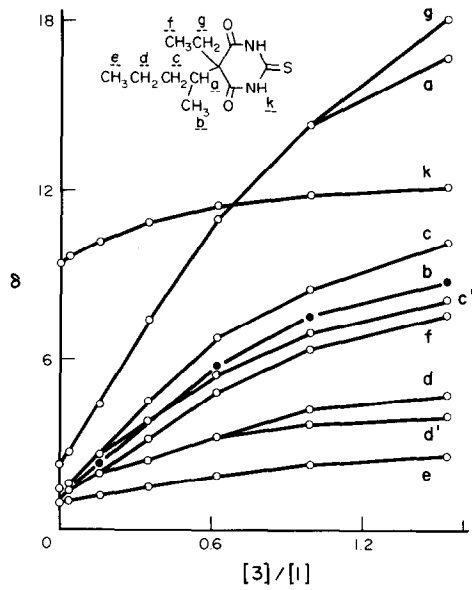


Figure 2
Variation of chemical shift, δ, with molar ratio of $Eu(TFC)_3$ to thiopental. Average values are plotted where antipodal differences occur.

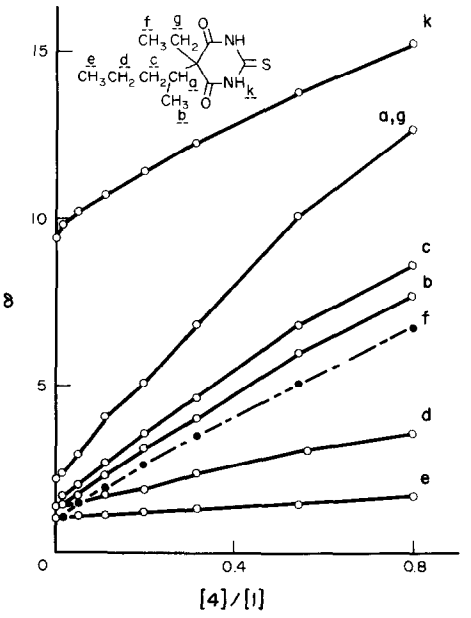


Figure 3
Variation of chemical shift, δ, with molar ratio of $Eu(HFC)_3$ to thiopental. Average values are plotted where antipodal differences occur.

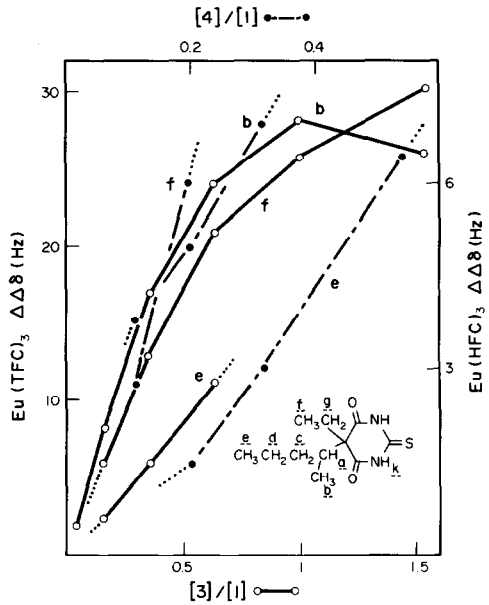


Figure 4
Variations of enantiomeric shift difference, $\Delta\Delta\delta$ (in Hz), with molar ratio of $Eu(TFC)_3$ or $Eu(HFC)_3$ to thiopental. $Eu(TFC)_3$ results are plotted with open circles and solid lines, according to the left hand and bottom axes. $Eu(HFC)_3$ results are plotted with filled circles and broken lines, according to the right hand and top axes. Extrapolated portions of lines are dotted.

oxobarbiturate analogues are summarized in Table 1, which presents chemical shift data for the substrates with no added shift reagents, in $CDCl_3$ solution. All substrates were free acids. The lanthanide-induced shifts, $\Delta\delta$, are the chemical shift values in the presence of LSR minus the shift value for the corresponding nucleus in the absence of LSR. These $\Delta\delta$ values are presented in Tables 2 and 3 for the reagents **2** and **3**, respectively. Data for **1** with **4** are included in Table 3. For uniformity in comparing these results, the $\Delta\delta$ (and $\Delta\Delta\delta$ values, if observed) are presented based on a shift reagent: substrate ratio of 0.5, extrapolated or interpolated from actual experimental values. The tabulated $\Delta\delta$ (and $\Delta\Delta\delta$) values, therefore, allow the analogous protons in this series of compounds to be considered based on correspondence of the proton locations.

In the simple 2-oxobarbituric acid derivatives, **5–8**, predominant LSR complexation is expected at the C_2 carbonyl based on electronic and steric factors. However, the europium(III) ion is usually regarded as a "hard acid" [39, 40] and would prefer to bind to oxygen rather than to sulphur [41–45]. In **1**, a 2-thiobarbituric acid derivative, major lanthanide binding would be expected to occur on the oxygens of the C_4 and C_6 carbonyls despite the steric hindrance resulting from 5,5-disubstitution. To the extent that bound lanthanide resides nearer these hindered carbonyls, the lanthanide would be closer to the chiral centre in the sidechain and potentially more likely to induce useful $\Delta\Delta\delta$ values. Observed $\Delta\delta$ values under the authors' conditions are expected to reflect fast exchange between bound and unbound lanthanide–substrate complexes [46, 47] corresponding to weighted averages of proton chemical shifts for the free substrate and for the substrate bound to europium. The greater fraction of substrate bound to lanthanide when complexation is possible at a hard base and relatively unhindered site, as in **5–8**, will be somewhat countered by greater $\Delta\delta$ values predicted because of proximity effects in **1**, in which Eu(III) is bound to a lesser degree but to sites that are closer to the sidechains. The change in preferred complexation sites would appear to be the single most crucial factor for all three thiobarbiturates (**1**, thiamylal and thiohexital) that leads to substantial

Table 1
Chemical shift data for indicated protons, in $CDCl_3$ at 28°C, 60 MHz ^1H spectra

Compound	Nucleus: a	b	c	d	e	f	g	h	i	j	k
1	2.13	1.03	1.30	1.10	0.93	1.00	2.13	—	—	—	9.42
5	2.13	1.03	1.33	1.10	0.88	0.98	2.13	—	—	—	9.32
6	2.08	1.03	1.47	0.82	—	0.91	2.08	—	—	—	8.73
7	2.20	1.08	1.35	1.13	0.93	—	2.80	5.60	5.07	5.17	9.08
8	2.07	1.07	1.57	0.92	—	—	2.80	5.63	5.05	5.20	8.67

Table 2
Approximate values of Δδ (in ppm) for designated protons based on a shift reagent: substrate ratio of 0.5,* using **2**. Average values for a diastereotopic pair may be presented for clarity unless separately listed

Compound	Proton resonances a	b	c,c′	d,d′	e	f	g,g′	h	i	j	k,k′
1	6.42	3.63	3.54, 4.36	1.80	0.66	3.01	5.90, 6.42	—	—	—	4.17
5	5.67	3.53	3.85	1.60	0.71	2.59	5.16, 5.67	—	—	—	4.69
6	3.76	2.33	2.32, 2.84	0.98	—	2.07	3.76	—	—	—	4.95
7	3.55	2.14	2.52	1.08	0.41	—	3.68	2.33	0.54	1.80	5.49
8	4.69	2.72	2.62, 3.68	0.89	—	—	5.13	3.29	0.99	2.49	5.77

* Interpolated or extrapolated from plotted curves.

Table 3
Approximate values of Δδ (in ppm) and ΔΔδ (in Hz) for selected protons based on a shift reagent: substrate ratio of 0.5,* using **3**. Values for ΔΔδ† are in parentheses. Average values for a diastereotopic pair may be presented for clarity unless separately listed

Compound	Proton resonances a	b	c,c′	d,d′	e	f	g,g′	h	i	j	k,k′
1	7.19	3.80 (20.6)	3.44, 4.42	1.59	0.78 (8.4)	2.92 (18.1)	7.24	—	—	—	2.06
‡	7.12	3.84 (9.5)	4.22	1.53	0.79 (6.0)	3.12 (15.1)	7.18	—	—	—	4.72
5	5.93	3.53	3.92	1.75	0.90 (3.7)	2.38	5.93	—	—	—	2.28
6	5.02	2.85	2.67, 3.28	1.25, 1.43	—	2.21	5.02	—	—	—	2.61
7	4.60	2.70 (9.5)	3.13	1.29	0.48	—	5.10	2.36	0.62	1.77	2.08
8	3.74	2.12	1.61, 2.34	0.69	—	—	4.11	1.87	0.46	1.57	2.01

* Interpolated or extrapolated from plotted curve.

† Deviations from linearity of some ΔΔδ plots and a relatively small number of experimental points for which ΔΔδ was measurable may cause errors in extrapolated values. An unlisted entry for ΔΔδ may indicate a zero value or a non-zero value rendered uncertain because of peak broadening or multiplicity.

‡ Values in this line refer to runs with **1** using **4**.

$\Delta\Delta\delta$ values for nuclei in the 5-alkyl sidechains. This present work allows direct comparison of the compounds **1** and **5**, which differ only in the heteroatom at C_2. Observed results are quite consistent with the analogous pair, thiamylal and **7**. One might generalize that chiral LSRs should permit direct optical purity determinations for those barbiturates in which the chiral centre is not part of the pyrimidine ring so long as lanthanide complexation can be steered close to the sidechain chiral centre, as in the 2-thio compounds.

Further supporting evidence for this suggestion is seen in results with **1** using **2**, **3** or **4**, in which observed $\Delta\delta$ values are greater for protons H_a, H_b, H_f and H_g than for any other substrate. These are the nuclei that would most be influenced by lanthanide bound at the proximal C_4 or C_6 oxygens. The protons H_d and H_e of **1** do not display especially large $\Delta\delta$ relative to the oxo-analogue compound **5**. The greater distance of $H_{d,e}$ compared to, e.g. $H_{a,b}$ results in a sharp dropoff in $\Delta\delta$ magnitude because of the r^{-3} dependence of the distance contribution [48]. As a result, in the thiobarbiturate **1** there is more of a variation in this r^{-3} term for the "close" compared to the "distant" nuclei than in the oxobarbiturates. In the latter compounds, with lanthanide complexed at the C_2 oxygen, there is a less dramatic change in the distance from the "close" protons $H_{a,b}$ compared to the "distant" $H_{d,e}$ since all of the nuclei are further from the europium. Only the greater fraction of bound substrate resulting from the less hindered C_2 oxygen binding compensates for the larger distance between proton and metal.

In comparing $\Delta\delta$ values for the NH resonances, it is seen that reagent **2** produces considerably larger values than **3** for all cases. Reagent **4**, however, a stronger Lewis acid (but bulkier) analogue of **3**, produced NH $\Delta\delta$ values with **1** that were comparable to values seen with **2**. The two diastereotopic NH proton signals were never separated by any of the shift reagents; substantial peak broadness may have contributed to this. The $\Delta\delta$ values for the NH protons of **1** with **2** or **3** generally appear among the lowest of the substrates reported here. Lanthanide complexation at the C_2 oxygen of the oxobarbiturates maintains the europium relatively close to both of the NH protons. In contrast, the europium would be divided between complexation at the C_4 and C_6 oxygens of the thiobarbiturates. Binding at either of these latter sites places europium close to one NH but far from the other. On average, a greater distance to the europium would be expected, consistent with the somewhat smaller $\Delta\delta$ values.

Although $\Delta\delta$ values for carbon-bound protons of **1** with **3** or **4** were very similar, $\Delta\Delta\delta$ values were substantially better with **3**, making it the reagent of choice for direct optical purity determinations of **1**. A **3**:**1** molar ratio of about 0.36 would be optimal. Consistent trends in $\Delta\delta$ values of carbon-bound protons using reagents **2** or **3** are not obvious. Larger $\Delta\delta$ values for carbon-bound protons are seen for **5** versus **6** with **2** or **3**, and for **7** versus **8** with **3** but not **2**. A simple prediction might have suggested that the larger alkyl substituent, 2-methylbutyl relative to 2-methylpropyl, should sterically impede lanthanide binding; this would lead to larger expected $\Delta\delta$ values for **6** and **8**, which generally was not seen. The authors rule out adventitious differences in LSR activities as a possible cause since relative $\Delta\delta$ values of the NH protons do not parallel those for CH protons. The larger group seems to favour induced shifts for carbon-bound protons (except for **7**/**8** with **2**) which might be consistent with longer lanthanide residence times for the complexes involving the larger substituent or a greater contribution from van der Waals attractions between shift reagent and substrate when the larger group is present. The reversal for **7** and **8** with **2** may represent a "crossover point" at which steric concerns have begun to outweigh these other factors. It is

interesting that for thiohexital, a 2-thiobarbiturate with a 1-methyl-2-pentynyl substituent at the 5-position, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] praseodymium(III), the praseodymium analogue of **4**, produced nearly twice as large a $\Delta\Delta\delta$ value for the distal 5-CH_3 than for the proximal 1-CH_3 of this sidechain [13]. It may be that specific interactions between a sidechain or substrate with an LSR might favour conformations that lead to unexpectedly favourable positions relative to the lanthanide, causing anomalously large $\Delta\delta$ or $\Delta\Delta\delta$ values for certain nuclei. For example, LSR studies of chloroquine indicated a complex in which a sidechain was curled back over the plane of a quinoline ring [49].

Actual representative spectral results are shown in the final figures. The unshifted reference spectrum of **1** is presented in Fig. 5. Figures 6(a) and 6(b) show typical spectral simplification for **1** in the presence of the achiral shift reagent, **2**, using **2**:**1** molar ratios of 0.579 and 0.842, respectively. Figure 7 shows the clear enantiomeric shift differences observable for each of the three methyl groups of racemic **1** using the chiral shift reagent **3**; the **3**:**1** molar ratio is 0.359.

Conclusions

Detailed results of studies of spectra with thiopental using achiral and chiral shift reagents have been described. Potential analytical utility for direct optical purity determinations of **1** using the chiral **3** has been demonstrated. Comparison data are presented for the 2-oxo analogue of thiopental as well as for other closely related oxo-

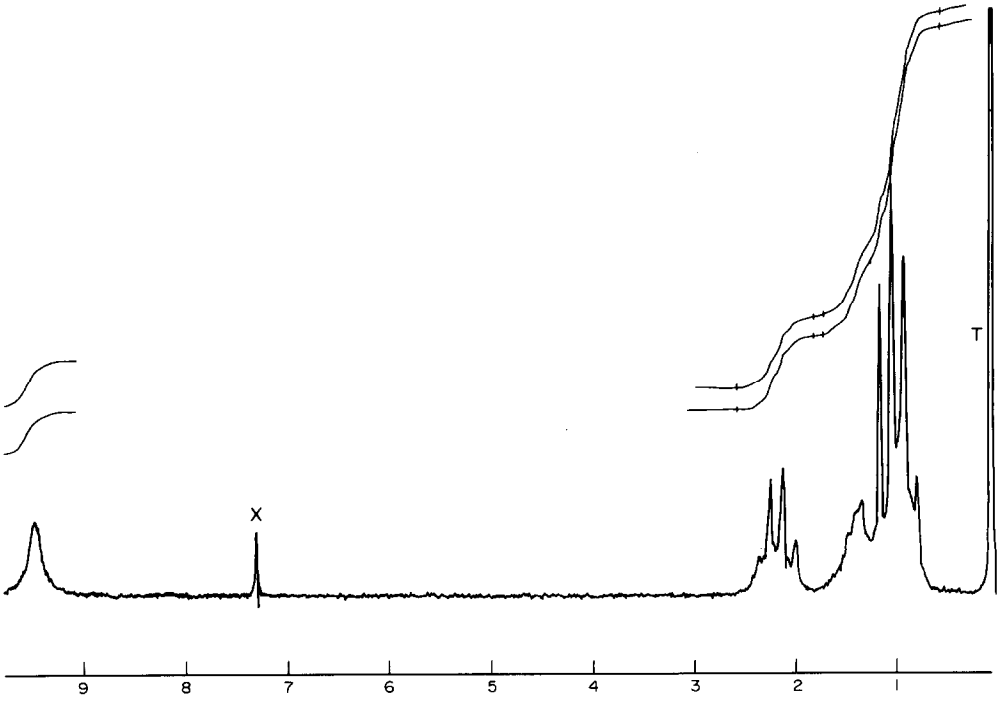


Figure 5
Standard reference ^{1}H NMR spectrum of thiopental, **1** (unshifted) at 28°C, 0.164 molal in $CDCl_3$ (X = $CHCl_3$ impurity in solvent; T = TMS).

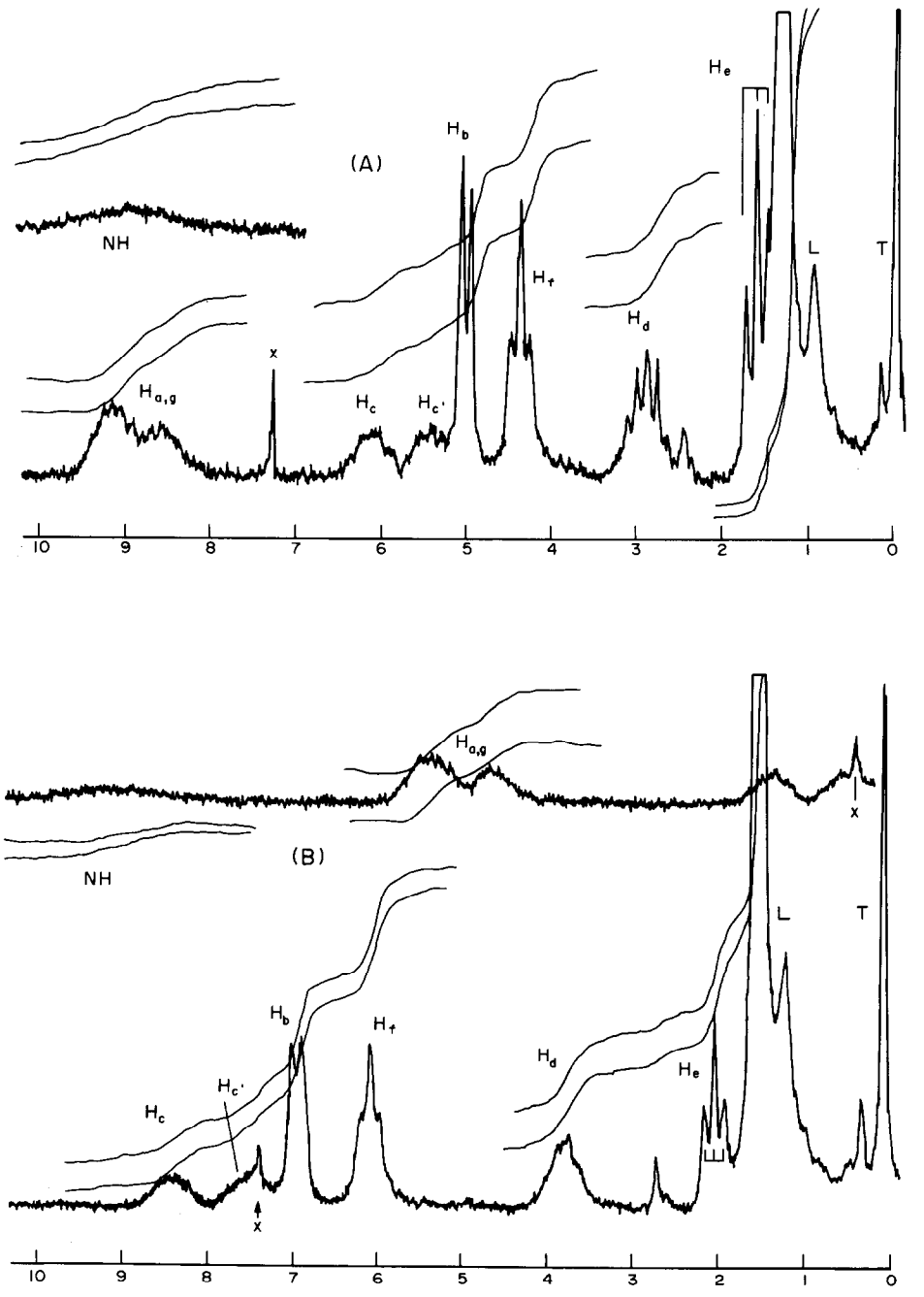


Figure 6
Representative spectra of **1** shifted by $Eu(FOD)_3$. (a) Shift reagent: **1** molar ratio of 0.579 with upper trace offset 5 ppm; (b) shift reagent: **1** molar ratio of 0.842 with upper trace offset 7 ppm. Concentration of **1** is 0.164 molal (L = shift reagent).

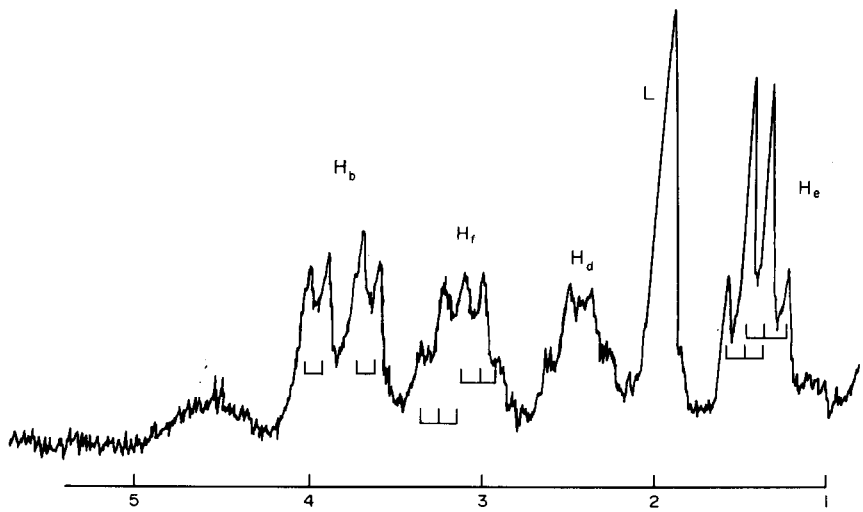


Figure 7
Representative spectrum of racemic **1** as 0.216 molal solution with added chiral shift reagent, Eu(FACAM)$_3$. Enantiomeric shift differences are indicated for enantiotopic nuclei. Spectrum was recorded on 5 ppm sweep width using a **3**:**1** molar ratio of 0.359.

barbiturates, in terms of unshifted reference spectral shifts for $CDCl_3$ solutions of the free acids, and $\Delta\delta$ and $\Delta\Delta\delta$ values for corresponding nuclei within this series of compounds. The data support a change in complexation site between thio- and oxobarbiturates, with lanthanide binding to the C_2 carbonyl in the latter and to the C_4 and C_6 carbonyls in the former. Relocation of lanthanide to binding sites that are more favourably disposed to the chiral centre and the alkyl sidechains results in larger $\Delta\Delta\delta$ values for thiobarbiturates. Chiral LSRs, such as **3**, appear to be generally useful for optical purity determinations for the thiobarbiturates, even if the chiral centre is not directly part of the pyrimidine ring, because of the change in binding sites relative to oxobarbiturates. Some aspects of relative $\Delta\delta$ and $\Delta\Delta\delta$ values for nuclei in this series suggest that a full understanding of these complex interactions must await further study.

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