3-viii: TLC on silica gel, R_f 0.85 (1:1 $CHCl_3$–AcOEt); mp 177 °C; IR (KBr disk) 3200, 1615 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.99 (d, 6 H), 2.1 (m, 1 H), 2.43 (s, 2 H), 2.66 (d, 2 H), 7.1–7.2 (m, 2 H), 7.70 (d, 1 H), 8.23 (m, 1 H), 8.9 (broad, 1 H).

3-x: TLC on silica gel, R_f 0.56 (10:1 $CHCl_3$–AcOEt); mp 228 °C; IR (KBr disk) 3150, 1585 cm^{-1}; NMR (Me_2SO-d_6) δ 2.43 (s, 3 H), 6.9–7.9 (m, 8 H), 8.15 (m, 1 H), 11.3 (broad, 1 H).

3-xi: TLC on silica gel, R_f 0.47 ($CHCl_3$); mp 175–177 °C; IR (KBr disk) 3250, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.36 (s, 9 H), 2.49 (s, 3 H), 6.8–7.2 (m, 2 H), 8.0–8.3 (m, 2 H), 11.5 (broad, 1 H).

General Procedure for Preparation of 2-Alkyl(or 2- Aryl)-indoles (4). A mixture of 215 mg (1.0 mmol) of 2-(pivaloylmethyl)-6-methylphenyl isocyanide (**2-xi**) and 3 mL of 10% HCl in methanol–water (1:1) was stirred for 15 min at room temperature. Then the mixture was made alkaline by adding 10% aqueous NaOH and stirring for 15 min at room temperature. The reaction mixture was extracted with ether, and the ether extract was evaporated. The residue was chromatographed on silica gel with $CHCl_3$ to afford 2-*tert*-butyl-7-methylindole (**4-xi**) in 82% yield: TLC, R_f 0.89; mp 98–99 °C; IR (KBr disk) 3425 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.29 (s, 9 H), 2.26 (s, 3 H), 5.90 (d, 1 H). 6.4–7.1 (m, 3 H), 7.3 (broad, 1 H).

4-iii: bp 115 °C (0.4 mm); IR (neat) 3390 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.88 (d, 6 H), 1.8 (m, 1 H), 2.27 (d, 2 H), 5.90 (m, 1 H), 6.7–7.2 (m, 4 H), 7.4 (broad, 1 H).

4-iv: mp 74–76 °C; IR (KBr disk) 3420 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.37 (s, 9 H), 6.18 (d, 1 H), 6.9–7.5 (m, 4 H), 7.8 (broad, 1 H).

4-v: TLC on silica gel, R_f 0.81 ($CHCl_3$); mp 61 °C; IR (KBr disk) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.83 (t, 3 H), 1.1–1.8 (m, 10 H), 2.60 (t, 3 H), 6.05 (m, 1 H), 6.8–7.4 (m, 4 H), 7.6 (broad, 1 H).

4-vi: TLC on silica gel, R_f 0.83 (20:1 $CHCl_3$–AcOEt); mp 177 °C; IR (KBr disk) 3425 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 6.72 (m, 1 H), 6.9–7.7 (m, 10 H), 8.3 (broad, 1 H).

4-vii: TLC on silica gel, R_f 0.53 (2:1 $CHCl_3$–benzene); mp 62–66 °C; IR (KBr disk) 3430 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.30 (s, 9 H), 5.97 (d, 1 H), 6.95 (m, 2 H), 7.30 (m, 1 H), 7.8 (broad, 1 H).

4-ix: TLC on silica gel, R_f 0.88 (1:1 $CHCL_3$–benzene); mp 101–103 °C; IR (KBr disk) 3420 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.34 (s, 9 H), 2.29 (s, 3 H), 5.93 (d, 1 H), 6.5–7.1 (m, 3 H), 7.4 (broad, 1 H).

4-x: TLC on silica gel, R_f 0.80 ($CHCl_3$); mp 216–217 °C; IR (KBr disk) 3420 cm^{-1}; NMR (Me_2SO-d_6 with Me_4Si) δ 2.30 (s, 3 H), 6.46 (d, 1 H), 6.7–7.6 (m, 8 H), 10.7 (broad, 1 H).

Registry No.—**2-i,** 69622-45-3; **2-ii,** 69622-46-4; **2-iii,** 69622-47-5; **2-iv,** 69622-53-3; **2-v,** 69622-48-6; **2-vi,** 69622-49-7; **2-vii,** 69622-55-5; **2-viii,** 69622-50-0; **2-ix,** 69622-51-1; **2-x,** 69622-52-2; **2-xi,** 69622-54-4; **3-i,** 703-80-0; **3-ii,** 22582-67-8; **3-iii,** 69622-34-0; **3-iv,** 69622-35-1; **3-v,** 69622-36-2; **3-vi,** 15224-25-6; **3-viii,** 69622-37-3; **3-x,** 69622-38-4; **3-xi,** 69622-39-5; **4-iii,** 3623-86-7; **4-iv,** 1805-65-8; **4-v,** 54687-20-6; **4-vi,** 948-65-2; **4-vii,** 69622-40-8; **4-ix,** 69622-41-9; **4-x,** 13228-36-9; **4-xi,** 69622-42-0; $CH_3CO_2CH_2CH{=}CH_2$, 591-87-7; n-$C_3H_7CO_2$-$CH_2CH{=}CH_2$, 2051-78-7; i-$C_4H_9CO_2CH_2CH{=}CH_2$, 2835-39-4; t-$C_4H_9CO_2CH_2CH{=}CH_2$, 15784-26-6; n-$C_7H_{15}CO_2CH_2CH{=}CH_2$, 4230-97-1; $PhCO_2CH_2CH{=}CH_2$, 583-04-0; 1-isocyano-2-methylbenzene, 10468-64-1; 4-chloro-1-isocyano-2-methylbenzene, 60515-59-5; 1-isocyano-2,4-dimethylbenzene, 3100-93-4; 2-isocyano-1,3-dimethylbenzene, 2769-71-3.

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Novel Synthesis of 3,4-Dihydro-1*H*-2,1,3-benzothiadiazine 2,2-Dioxides

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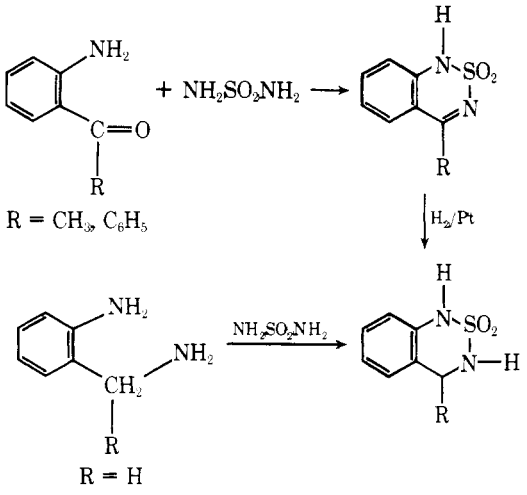
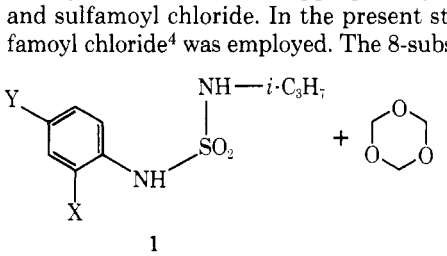
In 1965, Wright reported the first synthesis of 1*H*-2,1,3-benzothiadiazine 2,2-dioxides from the reaction of sulfamide with 2-aminobenzophenones and 2-aminoacetophenones.[1] Catalytic hydrogenation of the 1*H*-2,1,3-benzothiadiazine



2,2-dioxides in acetic acid solution using Adams catalyst gave the 3,4-dihydro derivative. 3,4-Dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides have also been prepared from the reaction of 2-aminobenzylamines with either sulfuryl chloride[2] or sulfamide.[3] We wish to report here a novel synthesis of 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides involving cyclization by intramolecular sulfonylamidomethylation. We have found that the reaction of trioxane with *N*-aryl-*N'*-alkylsulfamides in methanesulfonic acid–methylene chloride solution at ice bath to room temperature provides a facile method for the preparation of a number of the substituted title compounds (see Table I). The sulfamide precursors are readily available from the appropriately substituted aniline and sulfamoyl chloride. In the present study, isopropylsulfamoyl chloride[4] was employed. The 8-substituted derivatives



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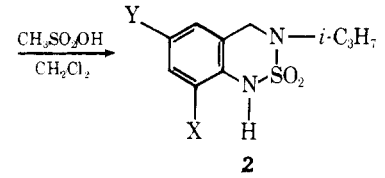

2

readily undergo nitration or bromination in the 6 position. In the presence of a tertiary base, the N–H moiety is acetylated.

A comparison of the present cyclization with the phenylmethanesulfonamide system described by Orazi and Corral is of interest.[5] The kinetic product **3** is obtained in 54% yield after 2 min at 35 °C whereas the thermodynamic product **4** was obtained in 67% after 3 h. The formation of a triazine was not observed in the present study. The trimerization of the

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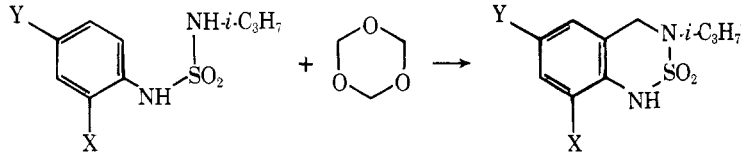
Table I. Preparation of 3,4-Dihydro-1*H*-2,1,3-benzothiadiazine 2,2-Dioxides

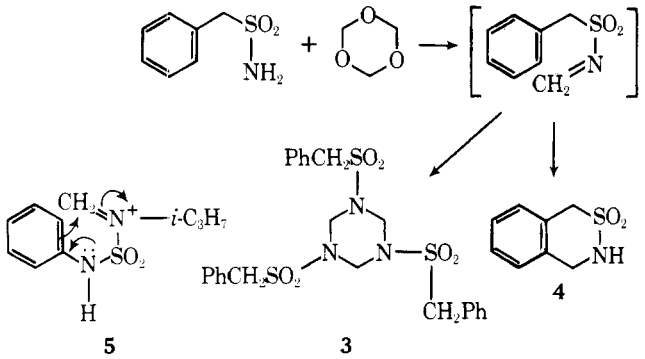


1 2

sulfamide	X	Y	thiadiazine[b]	mp, °C	recrystallization[a] solvent
1a	H	H	2a	106–108	A
1b	CH_3	H	2b	134–137	A
1c	F	H	2c	127–130	B
1d	Cl	H	2d	98–100	C
1e	Br	H	2e	88–89	A
1f	CF_3	H	2f	91–93	D
1g	NO_2	H	2g	130–132	D
1h	CH_3	Cl	2h	126–128	A
1i	H	COOEt	2i	156–157	B

[a] A, methylene chloride–hexane; B, chloroform–hexane; C, benzene–methanol; D, methanol. [b] Satisfactory elemental analyses (C, H, N) were obtained for all products.

proposed intermediate **5** is unlikely due to the quaternary nitrogen.



5 3 4

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 267 spectrophotometer. NMR spectra (δ expressed in parts per million) were taken on a Varian EM-360 instrument using tetramethylsilane as an internal standard. Satisfactory elemental analyses were obtained for all compounds.

General Procedure for the Preparation of *N*-Aryl-*N'*-(1-methylethyl)sulfamides. In a 1000-mL round-bottomed flask equipped with dropping funnel, condenser, thermometer, and mechanical stirrer were placed 600 mL of methylene chloride, 38 g (0.483 mol) of pyridine, and 45 g (0.483 mol) of aniline. The solution was cooled to 5 °C and 74 g (0.48 mol) of isopropylsulfamoyl chloride added dropwise maintaining the temperature under 10 °C. After the addition was complete, the reaction was allowed to come to room temperature. The reaction mixture was poured into a separatory funnel and washed with water and dilute hydrochloric acid. The organic extract was dried ($MgSO_4$) and filtered. The solvent was evaporated and the crude product recrystallized. In this manner, the following sulfamides were prepared (the solvent for recrystallization is given in parentheses): *N*-phenyl-*N'*-(1-methylethyl)sulfamide (**1a**), mp 97–98 °C (methylene chloride–hexane); *N*-tolyl-*N'*-(1-methylethyl)sulfamide (**1b**), mp 104–05 °C (methylene chloride–hexane); *N*-(2-fluorophenyl)-*N'*-(1-methylethyl)sulfamide (**1c**), mp 89–91 °C (methylene chloride–hexane); *N*-(2-chlorophenyl)-*N'*-(1-methylethyl)sulfamide (**1d**), mp 123–124 °C (methylene chloride–hexane); *N*-(2-bromophenyl)-*N'*-(1-methylethyl)sulfamide (**1e**), mp 118–119 °C (methylene chloride–hexane); *N*-(2-trifluoromethylphenyl)-*N'*-(1-methylethyl)sulfamide (**1f**), mp 73–74 °C (benzene–hexane); *N*-(2-nitrophenyl)-*N'*-(1-methylethyl)sulfamide (**1g**), mp 97–98 °C (benzene–methanol); *N*-(2-methyl-4-chlorophenyl)-*N'*(1-methylethyl)sulfamide (**1h**), mp 118–119 °C (methylene chloride–hexane); *N*-(4-carboethoxyphenyl)-*N'*-(1-methylethyl)sulfamide (**1i**), mp 130–32 °C (chloroform).

General Procedure for the Preparation of 3,4-Dihydro-1*H*-2,1,3-Benzothiadiazine 2,2-Dioxides. Sulfamide **1a** (26 g, 0.121 mol) was dissolved in a solution prepared from 250 mL of methylene chloride and 145 mL of methanesulfonic acid and cooled to 5 °C. *s*-Trioxane (3.64 g, 0.04 mol) was dissolved in 100 mL of methylene chloride and added rapidly to the sulfamide solution. The temperature increased to 15 °C. After the reaction cooled to ice-bath temperature, the mixture was poured onto ice–water and washed three times with water to remove residual methanesulfonic acid. The organic extract was dried ($MgSO_4$), filtered, and evaporated to give 27.7 g of crude product. Recrystallization from methylene chloride–hexane gave **2a:** mp 106–108 °C; NMR ($CDCl_3$) δ 1.07 (d, 6, N(3)-CH_3), 4.13 (m, 1, methine), 4.57 (s, 2, C-4), 6.50–7.25 (m, 5, aromatic and N(1)).

Bromination of 2a. 2a (1.0 g, 4.16 mmol) and *N*-bromosuccinimide (0.74 g, 4.16 mmol) were dissolved in 20 mL of methyl formate and stirred at room temperature for 4 h. The reaction mixture was diluted with methylene chloride, washed twice with water, dried, and evaporated. The crude material was recrystallized from methanol to give 3,4-dihydro-3-(1-methylethyl)-6-bromo-8-methyl-1*H*-2,1,3-benzothiadiazine 2,2-dioxide: mp 128–130 °C; NMR ($CDCl_3$) δ 1.12 (d, 6, N(3)-CH_3), 4.17 (m, 1, methine), 4.60 (s, 2, C-4), 6.67–7.50 (m, 3, aromatic and N(1)).

Anal. Calcd for $C_{11}H_{15}BrN_2O_2S$: C, 41.4; H, 4.7; N, 8.8. Found: C, 41.5; H, 4.85; N, 9.09.

Acetylation of 2a. 2a (2.4 g, 0.01 mol) and 1.4 mL of triethylamine were dissolved in 50 mL of benzene and acetyl chloride (0.78 g, 0.01 mol) in 10 mL of benzene was added dropwise to the thiadiazine solution. The product was isolated by extraction and recrystallized from chloroform–hexane to give 1-acetyl-3,4-dihydro-8-methyl-3-(1-methylethyl)-1*H*-2,1,3-benzothiadiazine 2,2-dioxide: mp 107–109 °C; NMR ($CDCl_3$) δ 1.11 (d, 6, N(3)-CH_3), 2.03 (s, 3, C(8)CH_3), 2.57 (s, 3, N(1) acetyl), 4.07 (m, 1, methine), 4.27 (s, 2, C(4)), 6.65–7.04 (m, 3, aromatic).

Nitration of 2a. 2a (4 g, 0.14 mol) was dissolved in 100 mL of acetic acid and added dropwise to 20 mL of 70% nitric acid. After being stirred for 1 h at room temperature, the mixture was poured into water and extracted with methylene chloride. Recrystallization from chloroform–hexane gave 3,4-dihydro-3-(1-methylethyl)-6-nitro-8-methyl-1*H*-2,1,3-benzothiadiazine 2,2-dioxide: mp 163–4 °C; NMR ($CDCl_3$) δ 1.16 (d, 6, N(3)-CH_3), 2.26 (s, 3, C(8)), 4.17 (m, 1, methine), 4.66 (s, 2, C(4)), 7.05 (br, 1, N(1)), 7.76 (d, 2, C(5) and C(7)).

Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.29; H, 5.30; N, 14.73. Found: C, 45.9; H, 5.35; N, 14.70.

Registry No.—**1a,** 69705-83-5; **1b,** 69705-84-6; **1c,** 69705-85-7; **1d,** 69705-86-8; **1e,** 69705-87-9; **1f,** 69705-88-0; **1g,** 69705-89-1; **1h,** 69705-90-4; **1i,** 69705-91-5; **2a,** 69705-92-6; **2b,** 69705-93-7; **2c,** 69705-94-8; **2d,** 69705-95-9; **2e,** 69705-96-0; **2f,** 69705-97-1; **2g,** 69705-98-2; **2h,** 69705-99-3; **2i,** 69706-00-9; aniline, 62-53-3; 2-methylbenzenamine, 95-53-4; 2-fluorobenzenamine, 348-54-9; 2-chlorobenzenamine, 95-51-2; 2-bromobenzenamine, 615-36-1; 2-(trifluoromethyl)benzenamine, 88-17-5; 2-nitrobenzenamine, 88-74-4;

4-chloro-2-methylbenzenamine, 95-69-2; ethyl 4-aminobenzoate, 94-09-7; *s*-trioxane, 110-88-3; 3,4-dihydro-3-(1-methylethyl)-6-bromo-8-methyl-1*H*-2,1,3-benzothiazine 2,2-dioxide, 69706-01-0; 1-acetyl-3,4-dihydro-8-methyl-3-(1-methylethyl)-1*H*-2,1,3-benzothiadiazine 2,2-dioxide, 69706-02-1; 3,4-dihydro-3-(1-methylethyl)-6-nitro-8-methyl-1*H*-2,1,3-benzothiadiazine 2,2-dioxide, 69706-03-2.

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Synthesis and Structure of Substituted Bicyclo[4.2.1]nona-2,4-dienes[1]

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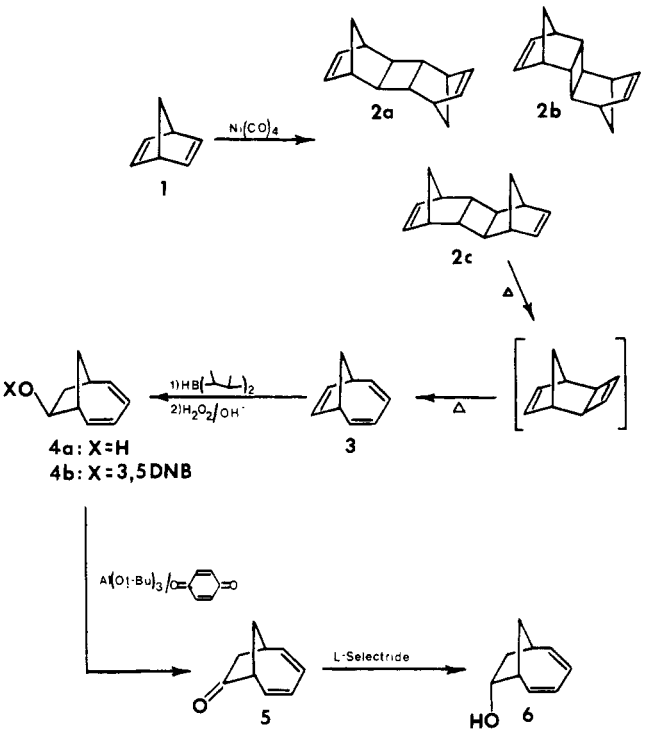
Previous work[2,3] has shown that certain rigid molecules lend themselves to complete structure elucidation by shift reagent techniques. These particular determinations were more readily performed than analysis by the more generally applicable but more operationally difficult method of X-ray diffraction. It was apparent to us that the conformationally rigid compounds **4a** and **5**, which served as intermediates in Masamune's total synthesis of methymycin,[4] and the endo alcohol **6**, also first synthesized by the Masamune group,[5] should be suitable candidates for complete structure determination by shift reagent methods. Moreover, we felt that these compounds, because of their high strain energy and the spatial proximity of the diene moiety to C-7, might show interesting chemical properties.

Although **4a** and **6** had been previously distinguished by determining the relative change in chemical shift of the two methylene bridge protons as a function of concentration of Eu(fod)$_3$,[5] this report details the complete structure assignment for **4a** and **6** and the partial assignment for **5** made possible by straightforward correlation between observed and calculated pseudo-contact shifts.[6] Use of Pr(fod)$_3$, which usually shifts proton resonances upfield with respect to tetramethylsilane, gave optimum separation of peaks. In addition, complete experimental details for the synthesis of **4a, 5,** and **6** as well as the precursorial triene **3** are presented for the first time.

Synthesis

Heating a mixture of **1** in benzene at 64–65 °C in the presence of Ni(CO)$_4$[7,8] yielded, after 2 days, a ~5:1 mixture of **2c** and **2b** in 60% yield but none of the difficulty pyrolyzable **2a**.[7] Since zero-valent cobalt compounds as used by Arnold[9] promote formation of **2a** almost to the exclusion of the other two trans dimers, the use of Ni(CO)$_4$ offers a real advantage. While the mechanism of the dimerization is not well understood, it seems reasonable to assume that the d orbitals of nickel interact with the π electron system of **1** to promote a reaction which is thermally disallowed in the absence of the metal.[10] The reaction, in our hands, did not involve a strictly catalytic interaction of Ni(CO)$_4$ with substrate, since an essentially stoichiometric amount of nickel compound was required. Moreover, it was observed that a shiny, metallic coating formed on the walls of the reaction apparatus as the reaction proceeded. Interestingly the reaction occurred at 65–70 °C but not at 50 °C.[11]

Scheme I



Pyrolysis of the dimer mixture at 400–430 °C gave **3** in 85% yield. This yield is higher than those reported previously,[5,7] and, more important, purification involved simple distillation only. Treatment of **3** with bis(3-methyl-2-butyl)borane[12a,b] followed by standard alkaline oxidative workup afforded **4a** in 61% yield. Oxidation to **5** in 75% yield required use of a modified Oppenauer oxidation[13a,b] since attempts using Cr(VI) under various conditions failed to produce ketone in significant amounts. Finally stereoselective reduction of **5** to give **6** (70%) was achieved using lithium tri-*sec*-butylborohydride.[14]

Shift Reagent Studies

The unshifted proton NMR spectra of **4a, 5,** and **6** were complex and not resolved due to overlapping of peaks in the methylene and diene proton regions. Use of Pr(fod)$_3$ as a shift reagent produced shifts to high field resulting in well-resolved spectra, while use of Eu(fod)$_3$, with its downfield shifts, was unsuccessful. The chemical shift of the various proton peaks was plotted vs. ρ, the ratio of concentration of shift reagent to substrate. These plots were essentially linear for **4a** and **6** in the range ρ = 0 to 0.4, whereas the plots for **5** were linear only in the range of ρ = 0 to 0.2. The observed lanthanide induced shifts, LIS, were taken as the slopes of the linear portion of the plots as determined by least squares, and the positions of peaks in the absence of shift reagent were given by the intercepts.

The calculated LIS values were obtained and compared with those observed using the PDIGM[15] approach as adapted for the IBM 1130 computer.[16] The minimum agreement or *R* factor, obtained by this approach for each molecule, is associated with the optimum geometry for the lanthanide atom with respect to the protons. Table I gives parameters relating to the optimum geometry for lanthanide complexes of **4a, 5,** and **6**. The *R* factors are sufficiently low as to place confidence in the results. To test the sensitivity of the method, calculations were run using the observed LIS values for exo alcohol with the coordinates for the protons of endo and vice versa,

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