thiocarbamate 4 (260 mg, 0.825 mmol), chloroacetone (85 mg, 0.92 mmol), potassium carbonate (185 mg, 1.34 mmol), and 25 ml of acetone were stirred at room temperature for 18 h. The solids were filtered and the filtrate was evaporated in vacuo. Chromatography of the residue from ca. 30 g of silica gel gave 145 mg (81%) of TLC pure thiazine **5** as an oil: IR 1720 cm^{-1}; NMR δ 2.24 (s, $CH_3C=$), 2.53 (s, SCH_3), 3.26 (s, SCH_2), 3.8 (s, OCH_3); *m/e* (70 eV) 217 (M^+). Thiazine **5** (120 mg, 0.55 mmol) and diphenylketene (50 mg, 0.26 mmol) in 5 ml of benzene were evaporated to a thin film in vacuo. This mixture was heated under N_2 in an oil bath at 110 °C for 2 h. TLC showed the presence of a new component. A further quantity of diphenylketene (50 mg in 5 ml of benzene) was added and the mixture was evaporated to a thin film in vacuo. This mixture was heated at 110 °C under N_2 for 2 h. The product was isolated by preparative TLC using benzene. A quantity of 27 mg of the thiazine **5** was recovered. Cephem **6** was a colorless solid: mp 168.5–170 °C dec (25 mg, 14% yield based on consumed thiazine); IR 1772, 1728 cm^{-1}; NMR δ 1.31 (s, SCH_3), 2.08 (s, $CH_3C=$), 3.09 (d, J_{gem} = 18 Hz, SCH_AH_B), 3.78 (d, J_{gem} = 18 Hz, SCH_AH_B), 3.87 (s, OCH_3), 7.2–7.85 (m, C_6H_5); *m/e* (70 eV) 411 (M^+), 365 ($M - SCH_3$). Anal. Calcd for $C_{22}H_{21}NO_3S_2$: C, 64.21; H, 5.14; N, 3.4. Found: C, 63.9; H, 5.09; N, 3.31.

Registry No.—**1**, 50917-77-6; **2**, 1067-74-9; **3**, 36016-40-7; **4**, 60762-07-4; **5**, 60762-08-5; **6**, 60762-09-6.

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(2) Syntex Postdoctoral Fellow, 1973–1974.
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Asymmetric Induction. Enantioselective Alkylation of Cyclohexanone

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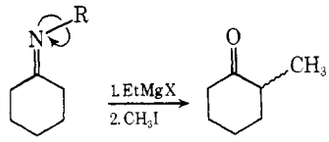
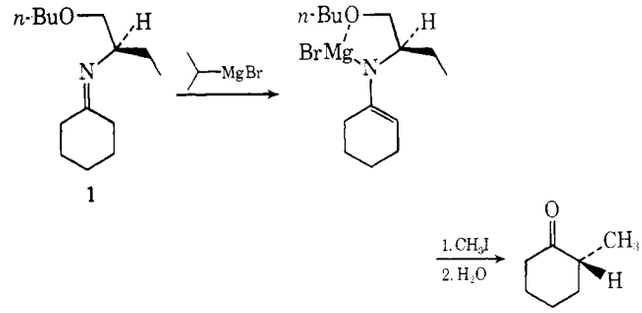
The field of asymmetric induction is one with a plethora of reported efforts but a dearth of actual techniques which lead to a high degree of enantioselectivity in a predictable manner.[1,2] We wish to report a sequence that accomplishes overall the α-alkylation of a ketone, providing a product with a high level of optical purity wherein the absolute configuration can be predicted with some degree of confidence.

The imine anion alkylation sequence of Stork[3] is one of the best techniques for achieving α-alkylation of ketones. The utilization of a chiral amine in forming the imine affords the opportunity for induction of asymmetry in the product, and though this approach has been examined with the cyclohexanone imine derived from isobornylamine, free rotation about the bond indicated would be expected to limit both the



level of and the predictability of the asymmetric induction.[4] We have directly addressed this problem by incorporating into the amine moiety a suitably situated ether oxygen so that *intra*molecular solvation of the metal ion will inhibit rotation. In particular, the *O*-*n*-butyl derivative of (*R*)-2-amino-1-butanol[5] was condensed with cyclohexanone to form the imine **1**. Conversion to the anion with isopropylmagnesium bromide in tetrahydrofuran and then alkylation at −78 °C with methyl



iodide led to (*R*)-2-methylcyclohexanone[6] with an optical purity of 81%. By effecting alkylation at −100 °C, the observed optical purity was increased to 85% while alkylation at reflux afforded the same sense of induction but with an optical purity of only 20%.

Experimental Section

(*R*)-2-Amino-1-butanol. This amine, as supplied by Aldrich Chemical Co. with $\alpha^{28}D$ −6.47° (neat, *l* = 1), was further resolved according to the known procedure.[5] One crystallization as the (+)-tartaric acid salt provided recovered amine with $\alpha^{20}D$ −9.38° (neat, *l* = 1) (lit.[5] max $\alpha^{20}D$ 10.1°, optical purity of 93%).

(*R*)-2-Aminobutyl *n*-Butyl Ether. A solution of 21 g (0.50 mol) of 57% sodium hydride in mineral oil in 200 ml of dimethyl sulfoxide was heated at 80 °C with mechanical stirring under an inert atmosphere for 1 h. To this warm solution was added 42.5 g (0.48 mol) of (*R*)-2-amino-1-butanol as purified above, the heating bath was removed, and the solution was cooled to room temperature, with stirring. After 1 h, the solution was cooled in an ice–water bath and 55 ml (0.51 mol) of *n*-butyl bromide was added over 20 min with vigorous stirring. The reaction mixture was stirred with cooling for an additional 1 h and then the semisolid mixture was washed out into a total volume of 1 l. of water. This solution was extracted with four 200-ml portions of ether, the combined organic layers were extracted with 400 ml of 2.0 N aqueous hydrochloric acid, and the aqueous layer was adjusted to pH 10 with solid potassium hydroxide and then extracted with two 200-ml portions of ether. These organic layers were combined, washed with saturated brine, dried with molecular sieves, concentrated, and then distilled in vacuo, affording 20.6 g (31%) of product, bp 102–106 °C (55 mmHg), $\alpha^{28}D$ −8.37° (neat, *l* = 1).

(*R*)-2-Methylcyclohexanone. The imine **1** was prepared by refluxing a solution of 20 mmol each of cyclohexanone and the amine above in benzene under an inert atmosphere for 12 h with azeotropic removal of water. The benzene was removed in vacuo and a solution of **1** in 5 ml of dry tetrahydrofuran was added under an inert atmosphere to a refluxing solution of 22 mmol of isopropylmagnesium bromide in 15 ml of the same solvent. After 2 h at reflux, the solution was cooled with a dry ice–acetone bath, and 27 mmol of methyl iodide was added dropwise over 15 min with vigorous stirring. The color changed from light yellow to off-white soon after the addition was complete. The reaction was held at −78 °C for a further 15 min, then warmed slowly to 0 °C at which point 11 ml of 2.0 N aqueous hydrochloric acid was added with vigorous stirring. After 15 min the mixture was diluted with 25 ml of pentane, and the organic layer was washed with dilute aqueous oxalic acid, 1 N sodium bicarbonate solution, then with two 20-ml portions of saturated brine. The organic layer was dried with molecular sieves, the solvents removed by distillation, and the residue distilled in vacuo, providing 1.17 g of material with $\alpha^{20}D$ −12.19° (neat, *l* = 1), consisting of 2-methylcycloxanone containing 3% of cyclohexanone (VPC, SE-30 column). After correction for both the presence of recovered cyclohexanone and the optical purity of the amine (93%), and using a maximum rotation[4,6] for 2-methylcyclohexanone of 16.75°, the optical purity was calculated as 81%.

Acknowledgment is gratefully made to the Research Corporation for financial support of this research.

Registry No.—**1**, 60662-02-4; (*R*)-2-amino-1-butanol, 5856-63-3; (*R*)-2-aminobutyl butyl ether, 60662-03-5; butyl bromide, 109-65-9; (*R*)-2-methylcyclohexanone, 22554-29-6; methyl iodide, 74-88-4; cyclohexanone, 108-94-1.

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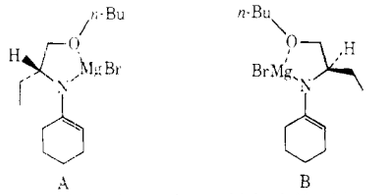

A B

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.

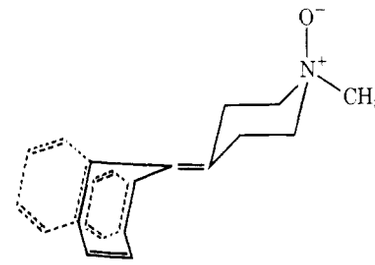
The ^{13}C NMR spectra of the two isomers provided evidence that the N-CH_3 group has the same orientation in both compounds since the chemical shift for the N-CH_3 group appeared at ca. 56 ppm in both isomers. These spectra were determined for the hydrochloride salts of the two isomers. In the ^{13}C 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

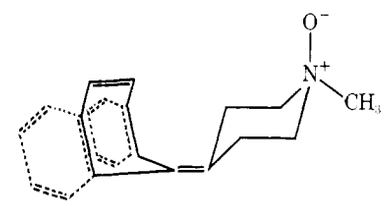
Isomer	δ_{1_H} (N-CH_3)[a]	δ_{1_H} (C_{10} + C_{11})[a]	δ_{13_C} (N-CH_3)[b]
α	3.12	6.88	56.2
β	3.28	6.88	56.0
α + LSR[c]		6.96[d]	
		7.02[e]	
β + LSR[c]		6.84[f]	
		6.78[g]	

[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°