Reduction of 1 with Catecholborane. To a tetrahydrofuran solution (10 mL) of catecholborane (240 mg, 2 mmol) was added a tetrahydrofuran solution (5 mL) of 1 (508 mg, 2 mmol) under nitrogen at 0 °C. The reaction was stirred at 0 °C for 3 h and then diluted with a saturated K_2CO_3 solution (10 mL). The reaction mixture was extracted with ether (3 × 25 mL), the ether extracts were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to give 480 mg of a dark brown oil. Chromatography (25% EtOAc/Skelly B) afforded 330 mg of a 7:1 mixture (determined by NMR) of **2** (56%) and **9** (10%): R_f 0.52 for **2** in 25% EtOAc/Skelly B; R_f 0.49 for **9** in 25% EtOAc/Skelly B.

Registry No. **1a**, 33868-76-7; **1b**, 13636-88-9; **1c**, 56944-71-9; **1d**, 78018-43-6; **2a**, 78018-44-7; **2b**, 19063-71-9; **2c**, 78018-45-8; **2d**, 78018-46-9; **3**, 19607-10-4; **4**, 78018-47-0; **5**, 61402-25-3; **6**, 78018-48-1; **7**, 78018-49-2; **8**, 78018-50-5; **9**, 78018-51-6; DIBAL·TEA complex, 78019-42-8.

Ultrasound in Heterogeneous Organic Reactions. An Improved Procedure for the Synthesis of Thioamides

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Thioamides are an interesting class of organic compounds which have been utilized in a variety of synthetic transformations,[1] including several methods for the selective reduction of amides to amines.[2] A thioamide is normally prepared by refluxing the corresponding amide with excess P_4S_{10} in various solvents.[1] Since the reaction is heterogeneous in nature, it usually requires a large excess of P_4S_{10} and it must be carried out for prolonged times. An alternative procedure for the conversion of amides to thioamides utilizing the dimer of *p*-methoxyphenylthionophosphine sulfide in toluene at 100 °C has recently been reported.[3] Both of these procedures suffer, however, from the high temperatures and prolonged reaction times necessary in order to carry out the transformation.

We now report that the rate of conversion of amides to thioamides is dramatically increased by irradiation of the reaction mixture in the water bath of an ultrasonic laboratory cleaner.[4] Typically, a solution of the amide in dry THF (0.1 M) is treated with 1–1.5 equiv of P_4S_{10} and irradiated in an ultrasonic laboratory cleaner bath at 30–40 °C for 1–2 h with efficient stirring. When no more starting material is detected by thin-layer chromatography, the reaction is worked up and the residue is purified by flash chromatography[5] with methylene chloride followed by crystallization. The thioamides are obtained in good to excellent yields by this procedure.

The advantage of this procedure over previous thioamidation methods include the shorter reaction times (1–2 h), the lower reaction temperatures (30–40 °C), and the elimination of the requirement for large excesses of P_4S_{10}. This procedure should prove to be particularly useful for the preparation of thioamides in systems containing other sensitive functionality.

We are currently examining the acceleration of a number of other heterogeneous reaction by the use of ultrasonic irradiation,[4] and we will report our results in due course.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Proton magnetic resonance spectra were obtained on a Varian EM-360L spectrometer and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. A Bransonic 12 bath sonicator (80 W) was used to generate ultrasonic irradiation.

The THF used in these experiments was distilled from sodium benzophenone ketyl, the P_4S_{10} was from a freshly open bottle (MCB Reagent), and the starting amides were either commercially available or prepared by standard methods.

General Procedure for Preparation of Thioamides. The amide (2.00 mmol) was dissolved in anhydrous THF (20 mL) in a 50-mL round-bottomed flask equipped with a magnetic stirring bar. The flask was placed in the water bath of the ultrasonic apparatus which contained a submerged, air-driven magnetic stirrer. To the reaction solution was added P_4S_{10} (445 mg, 1.0 mmol), the magnetic stirrer was started, and the reaction mixture was irradiated with ultrasound for 20–30 min. Within the first 15 min a nearly homogeneous solution was obtained, followed shortly by the formation of a white, phosphorous-containing precipitate. An additional portion of P_4S_{10} (445 mg, 1.0 mmol) was added to the mixture and sonication with efficient stirring was continued for an additional 30 to 90 min. If TLC indicated the presence of unreacted amide, another portion of P_4S_{10} (1.0 mmol) was added and irradiation was continued for 30 min. The final bath temperature never exceeded 40 °C. The heterogeneous mixture was cooled to ambient temperature and filtered. The solid byproduct was washed with several small portions of methylene chloride, the filtrates were combined, and solvents were removed in vacuo, giving a residue which was purified by flash chromatography[5] on silica gel 60 (40–63 μm) with methylene chloride to provide the thioamides which crystallized on standing.

***N*-Benzyl-2-thiopiperidone.**[2] Reaction of *N*-benzyl-2-piperidone by the above procedure afforded 315 mg (77%) of the thioamide: mp 25 °C; NMR ($CDCl_3$) δ 7.33 (s, 5 H), 5.27 (s, 2 H), 2.85–3.45 (m, 4 H), 1.50–1.90 (m, 4 H).

***N*,*N*-Dimethylthiobenzamide.** Reaction of *N*,*N*-dimethylbenzamide by the above procedure afforded 256 mg (78%) of the thioamide: mp 68–69 °C (lit.[6] mp 67 °C); NMR ($CDCl_3$) δ 7.35 (s, 5 H), 3.51 (s, 3 H), 3.07 (s, 3 H).

***N*,*N*-Dimethylthiophenylacetamide.** Reaction of *N*,*N*-dimethylphenylacetamide by the above procedure afforded 300 mg (84%) of the thioamide: mp 80–81 °C (lit.[6] mp 81 °C); NMR ($CDCl_3$) δ 7.34 (s, 5 H), 4.28 (s, 2 H), 3.45 (s, 3 H), 3.17 (s, 3 H).

***N*-Methylthiophenylacetamide.** Reaction of *N*-methylphenylacetamide by the above procedure afforded 304 mg (92%) of the thioamide: mp 61–63 °C (lit.[6] mp 63 °C); NMR ($CDCl_3$) δ 7.32 (s, 5 H), 4.06 (s, 2 H), 3.40 (d, 3 H).

***N*-Methylthioacetanilide.** Reaction of *N*-methylacetanilide by the above procedure afforded 351 mg (97%) of the thioamide: mp 57.5–58.5 °C (lit.[7] mp 59 °C); NMR ($CDCl_3$) δ 7.10–7.70 (m, 5 H), 3.72 (s, 3 H), 2.37 (s, 3 H).

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Registry No. *N*-Benzyl-2-thiopiperidone, 17642-89-6; *N*,*N*-dimethylthiobenzamide, 15482-60-7; *N*,*N*-dimethylthiophenylacet-

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amide, 17709-95-4; *N*-methylthiophenylacetamide, 77130-13-3; *N*-methylthioacetanilide, 5310-07-6; *N*-benzyl-2-piperidone, 4783-65-7; *N,N*-dimethylbenzamide, 611-74-5; *N,N*-dimethylphenylacetamide, 18925-69-4; *N*-methylphenylacetamide, 6830-82-6; *N*-methylacetanilide, 579-10-2; P_4S_{10}, 12066-62-5.

Stereospecific Synthesis of Optically Active Succinic-d_2 Acid

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Succinic-*d* acid has played a central role in the determination of configuration of molecules whose chirality is due to the presence of deuterium. It is readily available, easily purified, and has a high specific rotation in the ultraviolet region of the spectrum.[1]

(2*R*,3*R*)-(−)-Succinic-d_2 acid has previously been prepared by transformation of (4*R*)-4,5-dihydroxy-2-oxovaleric acid to 2-oxoglutaraldehydic acid by *Pseudomonas saccharophila* in D_2O.[2] Degradation afforded (−)-succinic-d_2 acid containing nearly two deuteriums and having nearly twice the rotation of (−)-succinic-*d* acid. To date, chemical synthesis of succinic-d_2 acid has been reported only as the racemate.[3]

During the course of some other investigations, a synthesis of optically active succinic-d_2 acid became necessary, both as an important intermediate, and as a means of estimating the optical purity of some related systems. We report here a stereospecific chemical synthesis of both enantiomers of succinic-d_2 acid from 2,3-dideuterio-2,3-dibromobutane-1,4-diol.

Results

The synthetic sequence which was employed is summarized in Schemes I and II. The synthesis and resolution of 2,3-dideuterio-2,3-dibromobutane-1,4-diol (Scheme I) was achieved by a slight modification of the procedures of Feit[4] and is described in the Experimental Section. Reduction of (2*R*,3*R*)-(+)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol ($[\alpha]^{20}_D$ +39.4° (*c* 2.9, methanol), mp 112–114 °C; lit.[4] for (2*R*,3*R*)-(+)-2,3-dibromobutane-1,4-diol) $[\alpha]^{20}_D$ +40.0° (*c* 2, methanol), mp 114.5 °C) with lithium aluminum hydride in THF followed by hydrolysis afforded a mixture which was not isolated but oxidized directly with potassium permanganate to (2*S*,3*S*)-(+)-2,3-dideuteriosuccinic acid. Mass analysis of succinic-d_2 anhydride derived from this acid by refluxing with acetic anhydride indicated that 1% undeuterated and 14% monodeuterated succinic acid was present. Proof that the lithium aluminum hydride reduction occurred stereospecifically was demonstrated by conversion to *trans*-1,2-dideuteriocyclobutane (Scheme II). No cis isomer could be detected by infrared spectroscopy[5] Inversion of configuration during hydride reduction was demonstrated by the fact that (2*R*,3*R*)-(+)-2,3-dibromodideuteriobutane-1,4-diol (absolute configuration related to L-threitol by Feit) gave (2*S*,3*S*)-(+)-dideuteriosuccinic acid. The absolute configuration of (2*R*,3*R*)-(−)-2,3-dideuteriosuccinic acid has been related to (*R*)-(−)-succinic-*d* acid by nonenzymatic methods by Portsmouth, Stoolmiller, and Abeles.[2]

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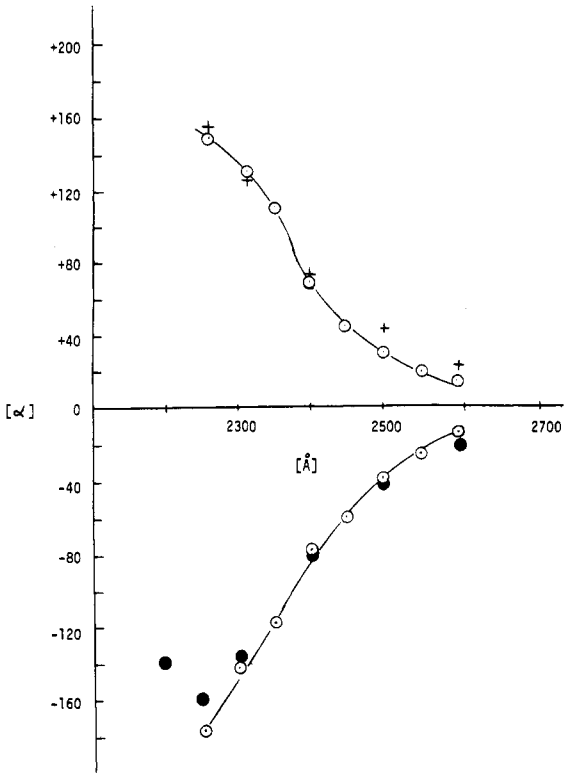

Figure 1. Circled dot, ⊙: for ORD curves for the following: (*R,R*)-(−)-2,3-dideuteriosuccinic acid from (*S,S*)-(−)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol ($[\alpha]^{20}_D$ −26.5°) corrected for optical purity and 14% (*R*)-(−)-deuteriosuccinic acid; (*S,S*)-(+)-2,3-dideuteriosuccinic acid from (*R,R*)-(+)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol $[\alpha]^{20}_D$ +39.4°) corrected for 14% (*S*)-(+)-deuteriosuccinic acid. Solid circle, ●: for ORD curve for (*RR*)-(−)-2,3-dideuteriosuccinic acid obtained from *Pseudomonas saccharophila* by Portsmouth et al.[2] The plus sign indicates values calculated for dideuteriosuccinic acid (2[α] for monodeuteriosuccinic acid).

Thus reduction with lithium aluminum hydride occurs stereospecifically and with inversion of configuration. The yield is estimated at 70%.

The optical rotatory dispersion (ORD) curves for both enantiomers of 2,3-dideuteriosuccinic acid are reported in Figure 1. The rotations have been corrected for optical purity (based on Feit's rotations for the corresponding bromo alcohols) and the isotopic distributions noted above. The contributions of succinic-*d* acid (14%) was assumed to contribute half the rotatory power of the dideuteriosuccinic acid in these calculations. The ORD curve reported by Portsmouth et. al.[2] for (−)-2,3-dideuteriosuccinic acid has been included for comparison in Figure 1 (solid circles). Agreement between the two curves is very good. Comparison of the observed curve to that generated by assuming the rotation of the (+)-dideuteriosuccinic acid

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