(Z)-4-(2-Methoxyvinyl)indole (7). To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (1.38 g, 4 mmol) in 5 mL of dry tetrahydrofuran was added 2.5 mL of a 1.6 M solution of *n*-BuLi in hexane. After 30 min at room temperature, a solution of indole-4-carboxaldehyde (0.29 mg, 2 mmol) in 4 mL of dry tetrahydrofuran was added dropwise at a rate such that the reaction temperature remained below 30 °C. After 1 h, 10 mL of water was added, and the reaction mixture was extracted with ether (4 × 10 mL). The ether extracts were dried ($MgSO_4$) and concentrated to afford a brown liquid. The crude product was chromatographed on neutral alumina with methylene chloride as eluent to yield 235 mg (73%) of **7**: mp 90–93 °C; IR ($CHCl_3$) 3500, 3025, 2950, 2900, 1640, 1410, 1350, 1275, 1200, 1160, 1100, 1080, 940 cm^{-1}; NMR ($CDCl_3$) δ 7.80–8.20 (br s, 1 H), 7.67 (t, 1 H, J = 4 Hz), 7.00–7.17 (m, 3 H), 6.43–6.70 (m, 1 H), 6.23 (d, 1 H, J = 7 Hz), 5.60 (d, 1 H, J = 7 Hz), 3.70 (s, 3 H); mass spectrum, m/e calcd 173.0841, obsd 173.0838.

Ethyl (E)-3-(4-Indolyl)propenoate (8). A solution of indole-4-carboxaldehyde (37 mg, 0.25 mmol) and [(carboethoxy)-methylene]triphenylphosphorane (175 mg, 0.50 mmol) in 2.5 mL of dry tetrahydrofuran was stirred at 50 °C for 24 h. The reaction mixture was concentrated, and the crude product was chromatographed on silica gel with 20% ethyl acetate–hexane as eluent to give 48 mg (89%) of **8**: mp 72–73.5 °C; IR ($CHCl_3$) 3450, 3000, 1690, 1625, 1280, 1230, 1195, 1182 cm^{-1}; NMR ($CDCl_3$) δ 8.02–8.34 (br s, 1 H), 7.94 (d, 1 H, J = 16 Hz), 6.98–7.34 (m, 4 H), 6.58–6.70 (m, 1 H), 6.46 (d, 1 H, J = 16 Hz), 4.18 (q, 2 H, J = 7 Hz), 1.32 (t, 3 H, J = 7 Hz); mass spectrum, m/e calcd 215.0946, obsd 215.0946.

(E)-4-(4-Hydroxy-3-methyl-1-butenyl)indole (9). To a suspension of (2-methyl-3-hydroxypropyl)triphenylphosphonium bromide (9 g, 20 mmol) in 100 mL of dry tetrahydrofuran cooled to −78 °C was added dropwise 26 mL of a 1.6 M solution of *n*-BuLi in hexane. The reaction mixture was brought to room temperature, and after 2 h, a solution of indole-4-carboxaldehyde (2.18 g, 15 mmol) in 15 mL of tetrahydrofuran was added to the red homogeneous solution of the phosphorane. After 20 h, the reaction mixture was poured into 100 mL of ethyl acetate and the mixture washed once with 200 mL of a saturated ammonium chloride solution and twice with 200 mL of a saturated sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The isolated crude product was chromatographed on silica gel with 25% ethyl acetate–hexane to yield 1.78 g (59%) of Wittig product **9**: IR ($CHCl_3$) 3550, 3450, 3000, 2975, 2900, 1710, 1405, 1350, 1210, 1050, 990 cm^{-1}; NMR ($CDCl_3$) δ 8.30 (br s, 1 H), 6.50–7.40 (m, 6 H), 6.17 (dd, 1 H, J = 16, 7 Hz), 3.57 (d, 2 H, J = 6 Hz), 2.60 (m, 1 H), 1.73 (br s, 1 H), 1.15 (d, 3 H, J = 6 Hz); mass spectrum, m/e calcd 201.1154, obsd 201.1154.

4-[1-Hydroxy-3-(1,3-dioxolan-2-yl)butyl]indole (12). To a flask containing 0.53 g (21.8 mmol) of magnesium foil (freshly washed with absolute ether and oven dried) covered with 15 mL of dry tetrahydrofuran was added 2.13 g (10.9 mmol) of 2-(2-bromo-1-methylethyl)-1,3-dioxolane. After being stirred 2 h at room temperature, the reaction mixture was cooled in an ice bath, and a solution of indole-4-carboxaldehyde (0.264 g, 1.82 mmol) in 2 mL of dry tetrahydrofuran was added by syringe. After 30 min, 20 mL of ether and 20 mL of saturated ammonium chloride were added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was chromatographed on silica gel with 40% ethyl acetate–hexane to yield 0.475 g (100%) of **12**: IR ($CHCl_3$) 3600, 3475, 2990, 2975, 2880, 1405, 1340, 1155, 1100, 1070, 940 cm^{-1}; NMR ($CDCl_3$) δ 8.56 (br s, 1 H), 7.18 (m, 4 H), 6.66 (m, 1 H), 5.30 (m, 1 H), 4.78 (d, 1 H, J = 5 Hz), 3.93 (m, 4 H), 1.00 (d, 3 H, J = 7 Hz); mass spectrum, m/e calcd 261.1365, obsd 261.1367.

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Registry No. 1, 1975-50-4; 2, 73816-11-2; 3, 39830-66-5; 4, 1074-85-7; 5, 1074-86-8; 6, 68900-05-0; 7, 73805-09-1; 8, 73805-10-4; 9, 73805-11-5; 10, 73805-12-6; 11, 73805-13-7; 12, 73805-14-8; methyl 2-methyl-3-nitrobenzoate, 59382-59-1; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; methyltriphenylphosphonium bromide, 1779-49-3; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7; [(carboethoxy)methylene]triphenylphosphorane, 1099-45-2; (2-methyl-3-hydroxypropyl)triphenylphosphonium bromide, 73805-15-9; 2-(2-bromo-1-methylethyl)-1,3-dioxolane, 33498-32-7; CH_3Br, 74-83-9; 2-isopropylidene-1,3-dithiane, 36998-38-6.

Product Stereospecificity in the Microbial Reduction of α-Haloaryl Ketones

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The importance of arene oxides as intermediates in the metabolism of aromatic compounds stimulated several studies on the absolute configurations of these compounds and of products from their enzymatic hydration.[1] The procedure used for determining the absolute stereochemistry of the diols formed on enzymatic hydration of the corresponding arene oxides of di- and tricyclic aromatic compound involved reducing the oxirane or diol to a hydroaromatic alcohol.[1b] The latter was then synthesized, resolved, and oxidized (after protecting the hydroxyl group) to a derivative hydroxy dicarboxylic acid of known configuration. In those instances, however, where the hydroaromatic alcohol is achiral, e.g., 2-indanol obtained from hydrogenolysis of *cis*- and *trans*-1,2-indandiol (metabolites of indene and 2-indanone), an alternative method of ascertaining the configuration is required. In the cases of *cis*- and *trans*-1,2-indandiol, microbial reduction of 2-bromoindan-1-one (**1a**) produced optically active *trans*-2-bromoindan-1-ol (**2a**) which was then stereospecifically converted to the two diols and indene oxide.[2] In addition to establishing the configurations of these metabolites, the presence of an α-bromo atom significantly increased the scope and potential value of microbially mediated ketone reductions. In continuing our studies of these carbonyl reductions, we have therefore examined the effect of an α-chloro atom as well as some stereochemical questions raised in the earlier study.[2,3] The compounds employed as substrates and the results are summarized in Table I.

These findings demonstrate that microbial reduction of α-haloaryl ketones generally yield halohydrins with enantiomeric excesses of 80% or more in good yield which serve as convenient intermediates for the preparation of optically active oxiranes. In addition, the intermediate halohydrin is frequently more useful than the oxirane in establishing the absolute stereochemistry at the benzylic carbon (see Figure 1). The presence of a heteroatom in the aromatic system does not appear to influence the

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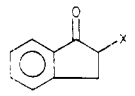
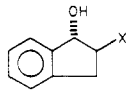
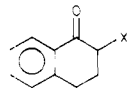
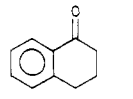
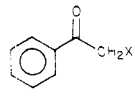
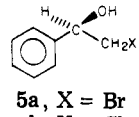
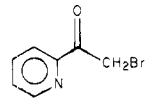
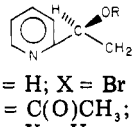
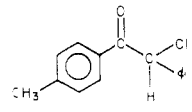
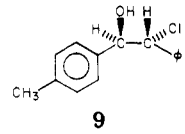
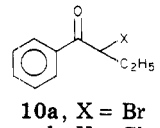
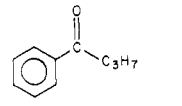
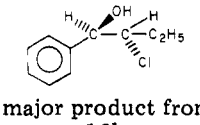
Table I. Microbial Reductions of α-Halo Ketones

substrate	product
 1a, X = Br b, X = Cl	 2a, X = Br b, X = Cl
 3a, X = Br b, X = Cl	
 4a, X = Br b, X = Cl c, X = H	 5a, X = Br b, X = Cl c, X = H
 6	 7a, R = H; X = Br b, R = C(O)CH$_3$; X = Br c, R = X = H
 8	 9
 10a, X = Br b, X = Cl	 major product from 10a
	 major product from 10b

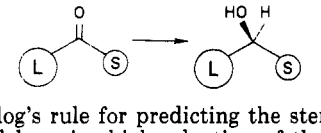


Figure 1. Prelog's rule for predicting the stereochemistry of alcohols formed by microbial reduction of the corresponding ketone.

stereochemical course of the reduction;[4] pyridyl ketones, e.g., are readily reduced. The lower molecular weights of the chloro compounds compared to those of the corresponding bromo ketones and the observation that (at least for compounds **10a** and **10b**) reductive cleavage occurs more readily with the bromo ketones make the chloro derivatives the preferred substrates.

Earlier studies[5a] had shown that the absolute stereochemistry of carbinols produced in microbial reductions could be predicted by Prelog's rule[5b,c] (Figure 1) from considerations of the relative sizes of the substituents flanking the carbonyl group. Microbial reduction in the synthesis of optically active halohydrins, as opposed to resolving diastereomeric halohydrins, possesses the advantage that the enantioselective reduction provides valuable information on the absolute stereochemistry of the product. In order to employ the rule shown in Figure 1 it is necessary to have an estimate of the size or bulk of the α-halomethine grouping. The absolute stereochemistries of **2a** and **2b** suggest that an α-halomethine in a cyclic ketone is "effectively larger" than the fused aromatic moiety. Attempts to test this conclusion by extending the study to the tetralone system, **3a** and **3b**, were unsuccessful, since reductive dehalogenation occurred.

When the acyclic ketones **4**, **6**, **8**, and **10b** were used as substrates, reduction to the corresponding halohydrin occurred. However, in rationalizing the configuration about the carbinol formed, with the help of Prelog's rule, it appears that mono- and disubstituted methyl groups are "effectively smaller" than an aromatic ring. In those cases where the α-carbon is potentially asymmetric, the two enantiomers are reduced at different rates.

In an earlier study of the microbial reduction of a series of benzil derivatives[6] it was found that the threo *R,R* diols were formed in high optical yields accompanied by benzoins enriched in the *S* enantiomer. These results were rationalized by proposing that the *R* enantiomer of the intermediate benzoin was reduced more rapidly than the corresponding *S* enantiomer. The reduction of **8** shows there is little difference in the effective size of chlorine atoms and hydroxyl groups in these reactions. Microbial reduction of a substituted benzoin[6] or the corresponding halogen derivative thus offers a synthetic route for the preparation of the corresponding optically active trans- or cis-substituted stilbene oxides, respectively.

In summary, introduction of an α-halogen into a variety of aryl ketones enhances the utility of microbial ketone reductions by making it possible to synthesize oxiranes, diols, and related derivatives and provides stereochemical information not available from alternative syntheses or resolutions.

Experimental Section

General Procedures. Melting points were determined by using a hot-stage apparatus; they are uncorrected. Proton magnetic resonance spectra were recorded on Varian HR-220 MHz instrument using Fourier transform techniques; chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard with coupling constants (*J*) in hertz. Optical rotations were recorded on a Cary 60 spectropolarimeter. Chemical-ionization mass spectra were taken with a Hitachi RMS-4 instrument. Microanalyses were performed by the Microanalytical Section of NIH. Preparative and analytical TLC work was performed on plates coated with silica gel F-254.

Microbial Reduction of α-Bromoacetophenone (4a). A 1-L Erlenmeyer flask containing 250 mL of a sterile solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was inoculated with *Cryptococcus macerans*.

The flask was shaken at 30 °C for 2 days, and to the opaque culture was added 100 mg of α-bromoacetophenone (**4a**). Shaking was continued for 7 days, and the suspension was then extracted three times with 250-mL portions of ethyl acetate. The ethyl acetate solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Analysis of the crude mixture by NMR indicated that 95% of the starting ketone had been converted into the alcohol. The alcohol was purified by thick-layer chromatography (silica gel; ethyl acetate–hexane, 15:85) to yield 81 mg (80% yield) of (−)-(*R*)-2-bromo-1-phenylethanol (**5a**), $[\alpha]^{25}_D$ −39° (*c* 8.00, $CHCl_3$). The NMR spectrum of this sample was identical with that of racemic material[7] prepared from styrene and *N*-bromo-

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(7) Robert P. Hanzlik, Marshall Edelman, William J. Michaely, and Georganna Scott, *J. Am. Chem. Soc.*, **98**, 1952 (1976).

succinimide: δ 3.50 (2 H, m), 4.14 (1 H, br s, OH), 4.82 (1 H, dd, J = 7.9, 4.8 Hz), 7.26 (5 H, m).

Conversion of (−)-(*R*)-2-Bromo-1-phenylethanol (5a) to (−)-(*S*)-α-Methylbenzyl Alcohol (5c). A solution of (−)-(*R*)-2-bromo-1-phenylethanol (20 mg) in acetic anhydride (5 mL) and pyridine (1 mL) was stirred at room temperature for 10 h. Water (20 mL) was added, and the mixture was extracted with benzene, washed with 5% HCl and 10% sodium bicarbonate, dried over anhydrous Na_2SO_4, and concentrated to yield (−)-(*R*)-2-bromo-1-phenyl-1-acetoxyethane which was purified by thick-layer chromatography on silica gel (ethyl acetate–hexane, 1:9): 19 mg (86%); colorless oil; $[\alpha]^{25}_D$ +54.1° (*c* 2.81, acetone). The NMR spectrum of this sample (in $CDCl_3$) was identical with that of racemic material: δ 2.10 (3 H, s), 3.59 (2 H, m), 5.97 (1 H, dd, J = 8.0, 5.0 Hz), 7.34 (5 H, m).

The (−)-acetate of **5a** (58 mg) was added to a slurry of $LiAlH_4$ (19 mg) in 10 mL of dry THF, and the solution was refluxed under N_2 for 5 h. The reaction mixture was decomposed with cold water and worked up as usual to yield a colorless oil which was purified by thick-layer chromatography (silica gel, ethyl acetate–hexane, 3:7) to give (−)-(*S*)-α-methylbenzyl alcohol (**5c**): 19 mg (79%); colorless oil; $[\alpha]^{25}_D$ −50.2° (*c* 5.11, $CHCl_3$); the optical purity was 93%, based on the absolute rotation reported in the literature.[8] The NMR of this sample was identical with that of racemic material.

Preparation of (*R*)-Styrene Oxide. A solution of (−)-**5a** (60 mg) in $CHCl_3$ (10 mL) and 2 N KOH (10 mL) was stirred at 40 °C for 3 h. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue purified by distillation (90 °C, 25 mmHg) to give (+)-(*R*)-styrene oxide: 28 mg (78% yield); $[\alpha]^{25}_D$ +42.2° (*c* 3.09, benzene). The NMR of this sample was identical with that of racemic material, and the optical purity was 95%, based on that of the authentic sample.[9]

Microbial Reduction of α-Chloroacetophenone (4b). When α-chloroacetophenone was subjected to the procedure described above for **4a**, the corresponding chlorohydrin was produced and purified by thick-layer chromatography (silica gel; ethyl acetate–hexane, 15:85) to yield (−)-(*R*)-2-chloro-1-phenylethanol: 80% yield; colorless oil; $[\alpha]^{25}_D$ −48.1° (*c* 1.73, C_6H_{12}). The optical purity was 100%, based on the specific rotation reported in the literature.[10]

The NMR spectrum of this sample was identical with that of racemic material prepared from styrene and *N*-chlorosuccinimide: NMR ($CDCl_3$) δ 3.00 (1 H, br s, OH), 3.58 (1 H, dd, J = 11.0, 8.5 Hz), 3.68 (1 H, dd, J = 11.0, 4.0 Hz), 4.82 (1 H, dd, J = 8.5, 4.0 Hz), 7.34 (5 H, m).

(−)-(*R*)-2-Chloro-1-phenylethanol was converted to (−)-(*R*)-2-chloro-1-phenyl-1-acetoxyethane by treatment with acetic anhydride–pyridine: colorless oil; $[\alpha]^{25}_D$ −53.8° (*c* 5.06, acetone); NMR ($CDCl_3$) δ 2.12 (3 H, s), 3.67 (1 H, dd, J = 11.5, 5.0 Hz), 3.76 (1 H, dd, J = 11.5, 7.8 Hz), 5.93 (1 H, dd, J = 7.8, 5.0 Hz), 7.35 (5 H, m).

Preparation of *p*-Methyldesyl Chloride (8). *p*-Methylbenzoin was prepared by the treatment of mandelonitrile with the Grignard reagent made from *p*-bromotoluene and Mg.[11]

Thionyl chloride (1 g) was added to a stirred solution of *p*-methylbenzoin (500 mg) in freshly distilled pyridine (0.5 mL). The solution was stirred for 5 h at 0 °C under N_2 and was then poured into ice–water (50 g). The reaction mixture was extracted with ether, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue purified by column chromatography over silica gel to yield 197 mg of *p*-methyldesyl chloride: pale yellow oil; NMR ($CDCl_3$) δ 2.34 (3 H, s), 6.32 (1 H, s), 7.14 (2 H, d, J = 8.9 Hz), 7.25–7.33 (5 H, m), 7.84 (2 H, d, J = 8.9 Hz).

Microbial Reduction of *p*-Methyldesyl Chloride. When *p*-methyldesyl chloride was subjected to the procedure described above for **4a**, analysis of the crude concentrate by NMR indicated that ~50% of the starting material had been converted to the *threo*-chlorohydrin. The stereochemistry was assigned by conversion to the *cis*-stilbene oxide as described below. For the *threo*-chlorohydrin: NMR ($CDCl_3$) δ 2.29 (3 H, s), 3.20 (1 H, br s, OH), 4.90 (1 H, d, J = 8.3 Hz), 4.99 (1 H, d, J = 8.3 Hz), 7.02–7.25 (9 H, m).

The absolute stereochemistry of the *threo*-chlorohydrin obtained was determined as 1*R*,2*R* by conversion to the (1*R*,2*S*)-*cis*-1-(4-methylphenyl)-2-phenylethylene oxide as follows. Without further purification, the crude microbial reduction product (100 mg) was treated with KOH (200 mg) in $CHCl_3$–H_2O (25 mL, 1:1 v/v) and stirred for 12 h at room temperature. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was subjected to thick-layer chromatography (silica gel; ethyl acetate–hexane, 1:9) to give the unreacted *p*-methyldesyl chloride (38 mg) and (+)-(1*R*,2*S*)-*cis*-1-(4-methylphenyl)-2-phenylethylene oxide: 17 mg; mp 28 °C; mass spectrum, m/e 210 (M^+); $[\alpha]^{25}_D$ +13.3° (*c* 3.10, EtOH); optical purity 90%, based on the absolute rotation.[11] CD Θ (λ) −7500 (227 nm), lit.[11] Θ (λ) −7670 (227 nm); NMR ($CDCl_3$) δ 2.21 (3 H, s), 4.30 (1 H, d, J = 4.2 Hz), 4.34 (1 H, d, J = 4.2 Hz), 6.94–7.17 (9 H, m). The NMR spectrum of this sample is identical with that of racemic material.[12]

Microbial Reduction of α-Bromobutyrophenone (10a). When α-bromobutyrophenone was subjected to the above procedure, analysis by NMR of the crude concentrate indicated a 2:1 ratio of starting material to butyrophenone (debromination product).

Microbial Reduction of α-Chlorobutyrophenone (10b). When α-chlorobutyrophenone was subjected to the procedure described above, analysis of the crude reaction mixture by NMR indicated that starting material, butyrophenone, and the corresponding chlorohydrin (a mixture of threo and erythro isomers) were produced in the ratio of 15:35:50. The reaction mixture was purified by thick-layer chromatography (silica gel; ethyl acetate–hexane, 3:7) to give a mixture of *threo*- and *erythro*-chlorohydrin. In order to examine the ratio of these two isomers, we treated this sample (100 mg) with KOH (200 mg) in $CHCl_3$–H_2O (25 mL, 1:1 v/v) and stirred it for 10 h at room temperature. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. Analysis of this reaction mixture by NMR indicated that the corresponding cis and trans epoxides were produced in the ratio of 90:10; no other products were detected. Both *cis*- and *trans*-1-phenyl-2-ethylethylene oxide were previously prepared by us, and their NMR data were reported.[13]

In order to examine the absolute configuration at a carbon bearing a hydroxy group, we converted the chlorohydrin so obtained (a mixture of threo and erythro isomers) to phenylpropylcarbinol as follows. A solution of the chlorohydrin (92 mg) in acetic anhydride (5 mL) and pyridine (1 mL) was stirred for 10 h at room temperature and worked up as usual to yield the corresponding chlorohydrin acetate quantitatively (checked by NMR and TLC). Without further purification, this sample was treated with $LiAlH_4$ (40 mg) in 10 mL of dry THF, and the solution was refluxed under N_2 for 5 h. The reaction mixture was decomposed with cold water and worked up as usual to yield a colorless oil which was purified by thick-layer chromtography (silica gel; ethyl acetate–hexane, 2:8) to give (−)-(*S*)-phenylpropylcarbinol: 53 mg (71% yield); colorless oil; $[\alpha]^{25}_D$ −24.1° (*c* 2.85, $CHCl_3$). An estimate of the optical purity of this sample can be made as 78.5% by assuming that the (−)-(*S*)-phenylpropylcarbinol ($[\alpha]^{25}_D$ −30.7° (*c* 2.60, $CHCl_3$)) prepared by the microbial reduction of butyrophenone[14,15] was optically pure.

Preparation of 2-(α-Bromoacetyl)pyridine (6). 2-Acetylpyridine was brominated in CCl_4 as described by Menassé et al.,[16]

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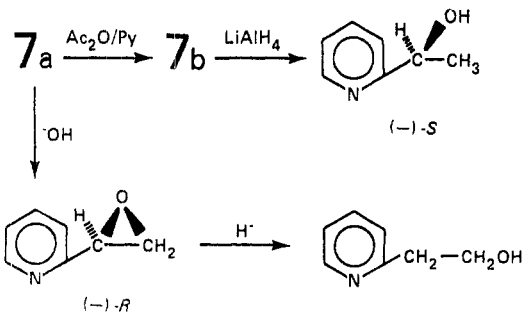
(11) P. M. Dansette, H. Ziffer, and D. M. Jerina, *Tetrahedron*, **32**, 2071 (1976).
(12) Mitsuru Imuta and Herman Ziffer, *J. Org. Chem.*, **44**, 2505 (1979).
(13) Mitsuru Imuta and Herman Ziffer, *J. Org. Chem.*, **44**, 1351 (1979).
(14) Microbial reduction of a sample of phenyl propyl ketone using *C. macerans* as described in ref 6 yielded (−)-(*S*)-phenylpropylcarbinol $[\alpha]^{25}_D$ −30.7° (*c* = 2.60, $CHCl_3$) (lit.[15] $[\alpha]_D$ (neat) −34.9°).
(15) P. A. Levene and A. Rother, *J. Org. Chem.*, **1**, 76 (1936).
(16) R. Menassé, G. Klein, and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 1289 (1955).

Scheme I



and the resulting **6** was purified by distillation: bp 110 °C (0.3 mm); NMR ($CDCl_3$) 4.88 (2 H, s), 7.55 (1 H, dd, J = 9, 5 Hz), 7.90 (1 H, dd, J = 9, 9 Hz), 8.10 (1 H, d, J = 9 Hz), 8.70 (1 H, d, J = 5 Hz).

Microbial Reduction of 6. To each of four flasks containing a 2-day-old shake culture of *C. macerans* was added 250 mg (total 1.0 g) of **6**. The flasks were shaken for 4 days. The combined aqueous phases were concentrated to half their original volume, made alkaline with $NaHCO_3$, and extracted with ethyl acetate. The organic layer was concentrated and the residue purified by thick-layer chromatography to yield 237 mg of **7a**, whose NMR spectrum was identical with that of an authentic sample prepared from 2-vinylpyridine by the procedure of Hanzlik et al.;[7] $[\alpha]^{25}_D$ −33.2° (*c* 4.06, $CHCl_3$).

Acetylation of (1*R*)-(2-Pyridyl)-2-bromoethanol (7a). The bromo alcohol **7a** (230 mg) was acetylated in the usual manner in pyridine–acetic anhydride (Scheme I) and purified by preparative thick-layer chromatography to yield 213 mg (77%) of the acetate, $[\alpha]^{25}_D$ −49.7° (*c* 1.45, $CHCl_3$). Its NMR spectrum was identical with one prepared from racemic **7a** by the same procedure.

$LiAlH_4$ Reduction of (1*R*)-(2-Pyridyl)-2-bromo-1-acetoxyethane (7b). An ether solution of (1*R*)-(2-pyridyl)-2-bromo-1-acetoxyethane (200 mg) was added slowly to an ether suspension of excess $LiAlH_4$ at 0 °C. The mixture was stirred for 2 h, decomposed with ice, and extracted with ether. The ether solution was dried and concentrated, and the residue was purified by thick-layer chromatography (EtOAc–hexane, 1:1) to yield 34 mg (34%) of (1*S*)-(2-pyridyl)ethanol (**7c**):$[\alpha]^{25}_D$ −49.8° (*c* 3.1, EtOH); ee 88%.[4]

Preparation of 2-Pyridylethylene Oxide. To a solution of **7a** (90 mg) in MeOH (7 mL) was slowly added 7 mL of 0.4 N NaOH at 0 °C and the mixture stirred for 1 h. The reaction mixture was extracted into ether, washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by thick-layer chromatography (EtOAc–hexane, 1:4) and distillation (bp 100 °C, 5 mm) to give (2*R*)-pyridylethylene oxide, $[\alpha]^{25}_D$ −15.0° (*c* 0.41, $CHCl_3$). The NMR spectrum was identical with that of racemic material.

Microbial Reduction of 2-Chloroindan-1-one (1b). When **1b** (500 mg) was subjected to the procedure described above for **4a**, 74 mg of the *trans*-chlorohydrin **2b** ($[\alpha]^{25}_D$ +16.5° (*c* 3.7, $CHCl_3$)) was isolated by thick-layer chromatography, and 424 mg of **1b** was recovered.

Conversion of (+)-2b to (1*R*)-Indanol. Acetylation of (+)-**2b** was carried out in the usual manner to yield 65 mg of the (+)-acetate, $[\alpha]^{25}_D$ +97.1° (*c* 1.4, $CHCl_3$).

A solution of the acetate in THF was refluxed overnight with excess $LiAlH_4$, and the resulting (*R*)-indanol (38 mg) was isolated by chromatography, $[\alpha]^{25}_D$ −13.3° (*c* 1.75, $CHCl_3$) (lit.[17] for (*R*)-indanol $[\alpha]^{25}_D$ −17° (*c* 5, $CHCl_3$).

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Registry No. **1b**, 73908-22-2; **2b**, 73951-59-4; **2b** acetate, 73951-60-7; **4a**, 70-11-1; **4b**, 532-27-4; **5a**, 73908-23-3; **5a** acetate, 73908-24-4; **5b**, 56751-12-3; **5b** acetate, 33942-01-7; **5c**, 1445-91-6; **6**, 40086-66-6; **7a**, 73951-61-8; **7b**, 73908-25-5; **7c**, 59042-90-9; **8**, 73908-26-6; **9**, 73908-27-7; **10a**, 73908-28-8; **10b**, 73908-29-9; (+)-(*R*)-styrene oxide, 20780-53-4; *p*-methylbenzoin, 66749-62-0; (+)-(1*R*,2*S*)-*cis*-1-(4-methylphenyl)-2-phenylethylene oxide, 62137-65-9; butyrophenone, 495-40-9; *threo*-1-phenyl-2-chloro-1-butanol, 73951-62-9; *erythro*-1-phenyl-2-chloro-1-butanol, 73951-63-0; *cis*-1-phenyl-2-ethyloxirane, 73951-64-1; *trans*-1-phenyl-2-ethyloxirane, 73951-65-2; (−)-(*S*)-phenylpropylcarbinol, 22135-49-5; (2*R*)-pyridylethylene oxide, 73908-30-2; (*R*)-indanol, 697-64-3.

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Protonation of Methoxyphenyl Alkyl Sulfides in Pentafluoroantimony-Fluorosulfonic Acid

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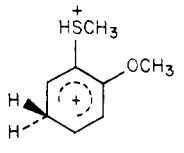
Aromatic sulfides protonate in strong acids exclusively at the sulfur atom,[2,3] unlike aromatic ethers[4,5] where the protonation sites involve both oxygen and ring carbon. The site of electrophilic attack in substitution reactions of alkoxy-substituted aromatic sulfides was found to be strongly affected by the presence of the alkoxy group.[6,7] It is, therefore, of considerable interest to examine the mode of protonation of these compounds. We present here some results on the protonation behavior of methoxyphenyl alkyl sulfides in SbF_5–FSO_3H solution.

o-, *m*-, and *p*-Methoxyphenyl sulfides (**1–3**, respectively) were protonated in 11.5 mol % SbF_5–FSO_3H at −80 °C. In addition, protonation of isomer **1** was carried out in pure FSO_3H solution. The site of protonation was determined on the basis of ^1H and ^{13}C NMR data of the ions formed, at −60 °C. The assignments of the ^{13}C resonances were made on the basis of their multiplicities in the off-resonance, ^1H-decoupled, ^{13}C NMR spectra and by comparison of their chemical shifts with the ^{13}C NMR chemical shifts of related positions in the *p*-methoxybenzenium ion[4] and the dimethyl phenyl sulfonium ion,[8] respectively.

The most interesting feature was exhibited by the ortho isomer. Its ^1H and ^{13}C NMR spectra are shown in Figures 1 and 2. The measured NMR data are best explaned by formation of a diprotonated species **4**.



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The ^1H NMR spectra (Figure 1, Table I) showed a well-resolved doublet at δ 3.36 (J = 7 Hz, total area 3) assigned to the SCH_3 protons, two partially overlapped

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