The Absolute Stereochemistry of α-Methylation in Benzyl Methyl Sulphoxide

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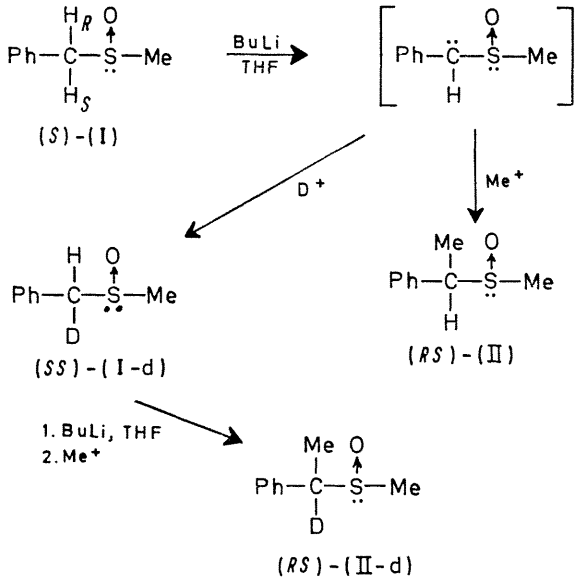
Summary Electrophilic substitution of benzyl methyl sulphoxide with methyl iodide has been shown to proceed with high stereoselectivity and with retention of the configuration (in tetrahydrofuran), in striking contrast to the partial deuteriation which appears to proceed with inversion.

DURST and his co-workers[1] have observed a remarkable solvent effect on the isomer distribution in the products obtained upon rapid quenching (with D_2O) of the carbanion generated from (*S*)-benzyl methyl sulphoxide (I), where the diastereomer having the (*SS*)-configuration was preferentially produced in solvents of low dielectric constant whereas the (*RS*)-sulphoxide predominated in dimethyl sulphoxide.



Since this result is contrasted with our own observation[2] of the solvent effect on the α-methylation of (*R*)-benzyl *p*-tolyl sulphoxide, we examined the absolute stereochemistry of the methylation in benzyl methyl sulphoxide.

(*R*)-Benzyl methyl sulphoxide, $[\alpha]_D$ −82·4° (*c* 3, EtOH), 78% optically pure,[3] was treated with 1 equiv of n-butyllithium (under nitrogen) in dry tetrahydrofuran at −70°. To the resulting solution containing the α-sulphinyl carbanion was added methyl iodide. After addition was complete, this was kept for 1 h at −70°, and, on the usual work-up, gave a diastereomeric mixture of α-phenethyl methyl sulphoxide (II). Inspection of the n.m.r. spectrum of the total crude product revealed that the diastereomer (IIa) having the MeSO at τ 7·85 (s, $CDCl_3$), α-Me (τ 8·30, d) CH (τ 6·18, q) preponderates (18·7:1)† over its epimer (IIb);‡ MeSO (τ 7·73,s), α-Me (τ 8·28, d), CH (τ 6·25, q). Under the nonequilibrating conditions of the experiment, (IIa) is the kinetically controlled major product. Oxidation of the methylated mixture with hydrogen peroxide in hot acetic acid gave the sulphone (III), m.p. 112—113°, $[\alpha]_D$ −29·5° (*c* 3, acetone).

Treatment of (*S*)-(−)-α-phenethyl chloride,§ $[\alpha]_D$ −60°, with MeSNa gave (*R*)-(+)-α-phenethyl methyl sulphide,[4] $[\alpha]_D$ +118° (neat, 10 cm), 60% optically pure. This was oxidized to (*R*)-α-phenethyl methyl sulphone, m.p. 112—113°, $[\alpha]_D$ +27·4° (*c* 4, acetone).

This sequence of reactions establishes that the configuration at carbon in (IIa) is (*S*). This agrees with our earlier result concerning the stereochemistry of the α-methylation of benzyl *p*-tolyl sulphoxide;[2] however, it is in direct contrast to Durst's result that the diastereomer (*SS*)-(I-d) was preferentially formed from (*S*)-(I) in tetrahydrofuran [*RS*-(I)/*SS*-(I) = 0·065 at −60°].[1]

In order to obtain further information concerning the stereochemistry, we studied the α-methylation of the carbanion derived from (*SS*/*RR*)-(I-d)¶,[1] (in tetrahydrofuran at −70°, BuLi as base), and found, on n.m.r. and m.s. analysis of the resulting total crude product, that α-deuteri-

† The ratios determined by n.m.r. analysis are accurate to within ±5%.

‡ Epimerization at sulphur does not occur under these conditions.[5] Proof of structural assignment was obtained by subsequent purification, and elemental and spectral analyses (n.m.r., i.r., m.s.). The material spectroscopically identical with (IIb) is predominantly produced by the peroxy-acid oxidation of α-phenethyl methyl sulphide and by the α-methylation of (I) in dimethyl sulphoxide.

§ Prepared by chlorination ($POCl_3$ in pyridine) of (*R*)-(+)-α-phenethyl alcohol, $[\alpha]_D$ + 38°, and used without further purification.

¶ Contaminated with 12% of (*RS*/*RS*)-(I-d) and 10% of nondeuteriated (I).

ated α-phenethyl methyl sulphoxide (*RS/SR*)-(II-d) was preferentially produced (78%). The existence of a small amount (22%) of the non-deuteriated (*RS/SR*)-(II-h) was observed, the amount of which corresponded to that of (*RS/SR*)-(I-d and -h) already present in the starting material (22%). The peak correspoding to the MeSO (τ 7·73 in $CDCl_3$) of (*RR/SS*)-(II), however, was 1/19 as strong as that of (*RS/SR*)-(II). Obviously, this is not the result of an isotope effect.[5a,5b]

This result therefore lends strong support for the above conclusion and defines the absolute stereochemistry of these reactions as shown.

The methylation proceeds with overall retention, whereas the reaction with deuterium cation appears to proceed with predominant inversion of the configuration, since both reactions must involve a common intermediate carbanion. The present result also indicates the preferential abstraction of the pro-(*R*) and -(*S*) hydrogen in (*S*)- and (*R*)-sulphoxides (I), respectively.

Our result also suggests the intervention of an α-sulphinyl carbanion of pyramidal structure; however, an alternative mechanism with a planar carbanion intermediate cannot be excluded at this time. This point, as well as the function of solvent, which undoubtedly plays an important role in determining the stereochemistry in electrophilic substitution reactions,[1,5a,6] is currently being investigated.

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