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STEREOCHEMISTRY OF THE ALKYLATION OF α-LITHIO THIEPANE AND THIOCANE 1-OXIDES

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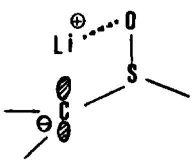
The reactions of α-lithio sulphoxides with electrophiles in THF are known to be highly stereoselective, the steric course depending on the nature of the electrophile. Thus methylation with CH_3I on the one hand (1), and deuteration (1), carbonylation (2), and carbonation (3) on the other, predominantly occur with opposite stereochemistry, giving products of anti and syn attack, respectively, with respect to the S-O bond. The findings that the stereochemistry of such reactions can be drastically affected by a solvent change (4), by the addition of macrocyclic polyethers (5) or of Li salts (6), have lent support to the idea (7) that the stereochemistry may be largely governed by cation-carbanion interactions and more particularly by the ability of Li^+ to form a chelate structure, **1** , involving the carbanionic carbon and the sulphoxide oxygen (5). This chelate would undergo electrophilic displacement of Li^+ with predominant retention of configuration when the electrophile-donating species can itself act as a chelating agent, **2** , but with inversion when this capacity is lacking, **3** (8, 9). Strong support for these views has been provided by the experiments with non che-



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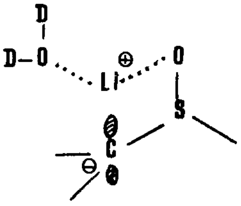

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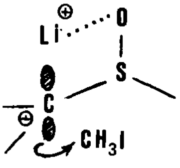

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lating proton donors (Et_3ND^+, D^+-sponge) (9) and with a chelating methylating agent /‾(MeO)$_3$PO_7 (8,9), where stereochemical courses have been evinced quite different from those normally observed.

The above is a convincing picture as it explains satisfactorily, if only qualitatively, all the results so far reported. Recently, however, we have made certain observations which appear to be at odd with the above theory. In the course of another research (10) we needed to synthetize 2-vinyl substituted thiacycloalkanes and chose to attach a two-carbon fragment to the position adjacent to the heteroatom by reacting the appropriate lithiated cyclic sulphoxide with oxirane. With α-lithio thiane 1-oxide the reaction took place readily at -70° in THF to give a single product which was unambiguously identified (^{13}C NMR) as the expected (11) trans-2-(2-hydroxyethyl)-thiane 1-oxide (10). However, with the α-lithio derivative of thiepane 1-oxide, while the reaction was so sluggish that the temperature had to be raised to 0°, two isomeric 2-(2-hydroxyethyl)-thiepane 1-oxides were obtained in a ~ 9:1 ratio, the more abundant isomer being assigned the cis configuration on the basis of ^{13}C NMR evidence (10).

This dependence of stereochemistry on ring size being novel, and unexpected on the basis of the current theory (8,9), it was important to know to what extent it was related to the nature of the oxirane electrophile and/or the temperature (4,9) at which this alkylation occurs with the 6-membered (-70°) (10) or with 7- and 8-membered α-lithio sulphoxides (0°) (10). To this end we have carried out the methylation of the 7- and 8-membered α-lithio sulphoxides with CH_3I in THF. The reactions occurred smoothly at -70° but the stereochemical results were substantially the same as in the alkylation with oxirane. The evidence is as follows. Quenching of α-lithio thiepane 1-oxide with excess CH_3I gave after work up a ~ 15:1 (12) mixture of 2-methylthiepane 1-oxides; the major isomer appears to be identical (chromatographic behaviour, ^1H NMR) to the minor isomer produced in the peroxy acid oxidation of 2-methylthiepane and which has been unequivocally assigned the cis configuration (13). The assignment is completely supported by the ^{13}C NMR spectra showing corresponding resonances to occur upfield in the major isomer. The chemical shifts (14) for the major and (in parentheses) the minor isomer, are as follows: C_2, 54.6 (60.0); C_3, 26.6 (30.3); C_4 or C_5, 25.1 or 26.4 (24.8 or 26.4); C_6, 17.6 (19.8); C_7, 48.1 (52.4); CH_3, 17.1 (17.2). The above differential shifts are (qualitatively) the same as those exhibited by the cis and trans pair of isomeric 1,2-dimethylthiepanium cations (15) in agreement with the notion that the S-O and S-CH_3 functions have similar ^{13}C NMR effects (16), and confirm the major sulphoxide has the cis configuration.

Methyl iodide quenching of α-lithio thiocane 1-oxide also gave two isomers (∼ 5:1) (12); again, corresponding ^{13}C resonances (14) occur upfield in the major isomer, indicating the latter has the cis configuration: C_2, 53.1 (58.7); C_3, 26.4 (29.7); C_4, C_5, or C_6, 24.4, 25.1, or 25.4 (23.8, 25.1 or 25.4); C_7, 19.9 (22.8); C_8, 47.2 (53.6); CH_3, 15.7 (16.7).

The results reported above are not such as to completely rule out Biellmann's and Marquet's mechanism; they show, however, the proposed mechanism is not entirely general and needs some additional particularization. A lead to further work may be sought in the reduced reactivity of the 7-membered α-lithio sulphoxides with respect to the 6-membered one (cf. the oxirane experiment) (17). This could indicate the departure of Li^+ from the larger rings is not, or is insufficently, assisted by the sulphoxide oxygen, due perhaps to the inability of these ring systems to achieve a conformation suitable for such assistance to occur. Thus electrophilic substitution from the front side may favorably compete.

The work is being extended to further substrates and electrophiles.

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