Epimerisation and Alkylation of a β-Thiolactone

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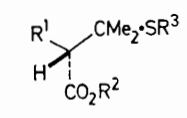
Summary Derivative (**3**) undergoes epimerisation at position 3 of its β-thiolactone ring when treated with triethylamine; alkylation occurs at the same site in the presence of a strong base and an alkylating agent.

IN connection with work aimed at the derivation of analogues of the β-lactam antibiotics, we wished to effect the alkylation of oxazoline-azetidinones of type (**1**) at position 2 of the butanoate group. Not surprisingly, when treated with NaH and MeI in tetrahydrofuran (THF), the methylthiobutanoate (**1**; $R^2 = R^3 = Me$)[1] was cleanly converted into the but-2-enoate (**2**).[1] We now report a solution to this problem which is likely to be of general value.

The hydrogen atom of the β-thiolactone ring in (**3**) is expected to be quite acidic. Moreover, the tendency towards β-elimination is likely to be markedly reduced in this derivative since the derived carbanion (**4**) possesses a near-orthogonal arrangement of the anionic centre and the

C–S bond. Consequently, (**3**) appeared to be a promising candidate for effecting the desired alkylation. Surprisingly, although it is established that thiol esters and γ-thiolactones[2] undergo alkylation adjacent to the carbonyl group, the corresponding reaction of β-thiolactones does not appear to have been reported.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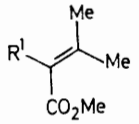
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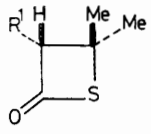
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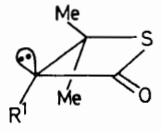
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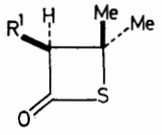
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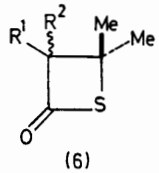
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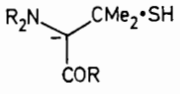
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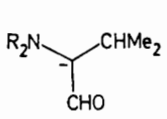
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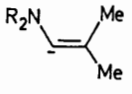
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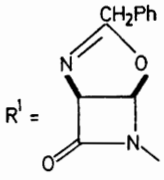

It is well known that β-mercapto-carboxylic acid salts are converted into β-thiolactones by reaction with ethyl chloroformate.[3] When treated with this reagent in pyridine, the mercury(II) salt (**1**; R^2R^3 = Hg)[4] afforded (42% after recrystallisation) the desired compound (**3**),† m.p. 129—131 °C, $[\alpha]_D$ −26° ($CHCl_3$).

The acidic nature of its β-thiolactone ring hydrogen atom was readily demonstrated by treating the derivative (**3**) with a drop of Et_3N in $CDCl_3$. A 1·5:1 mixture of the starting material and the epimer (**5**) [the derivatives were readily distinguished by the chemical shift of the β-thiolactone ring proton; that of the starting material appeared at δ 5·23 and that of the epimer (**5**) at δ 4·90] was rapidly formed. A similar mixture resulted when the pure epimer (**5**),† m.p. 158—162 °C, $[\alpha]_D$ + 121° ($CHCl_3$), was treated under corresponding conditions, establishing that the reaction was at equilibrium.

When treated with NaH and MeI in THF at 0 °C, the compound (**3**) afforded a *ca.* 1:1 mixture of the methyl derivatives (**6**; R^2 = Me). The mixture was separated by silica gel chromatography to give the more mobile epimer† (30%), m.p. 113—115 °C, $[\alpha]_D$ −60° ($CHCl_3$), and the less mobile epimer† (44%), m.p. 131—132 °C, $[\alpha]_D$ +178° ($CHCl_3$).

With potassium t-butoxide and t-butyl bromoacetate in *NN*-dimethylformamide at −20 °C, the compounds (**3**) or (**5**) afforded a *ca.* 6:1 mixture of the derivatives (**6**; R^2 = $CH_2{\cdot}CO_2Bu^t$). The major more mobile epimer,† m.p. 125—126 °C, $[\alpha]_D$ −60° ($CHCl_3$), was isolated [40% from (**3**) and 46% from (**5**)] after silica gel chromatography.

β-Thiolactones are known to react readily with nucleophilic reagents, always with cleavage of the S–CO bond. There are also reports of the derivatives undergoing desulphurisation with Raney nickel and thermal cycloreversion to alkenes and carbonyl sulphide.[3] In principle, the alkylation of β-thiolactones considerably increases their utility in synthesis, enabling the derivatives to be regarded as potential equivalents of the carbanions (**7**)—(**9**).

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† The composition of new compounds was confirmed by elemental analysis and/or by mass spectroscopy. Structural assignments are based upon i.r. and n.m.r. spectroscopic evidence.

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[2] J. Wemple, *Tetrahedron Letters*, 1975, **3255**; R. A. Gorski, G. J. Wolber, and J. Wemple, *ibid.*, 1976, 2577.
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[4] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181.