New Stereospecific Routes to Both Epimers of 2-Methyl-3-oxo- and 3-Methyl-2-oxo-steroids *via* 2-Lithio-1,3-dithian–Epoxide Reactions

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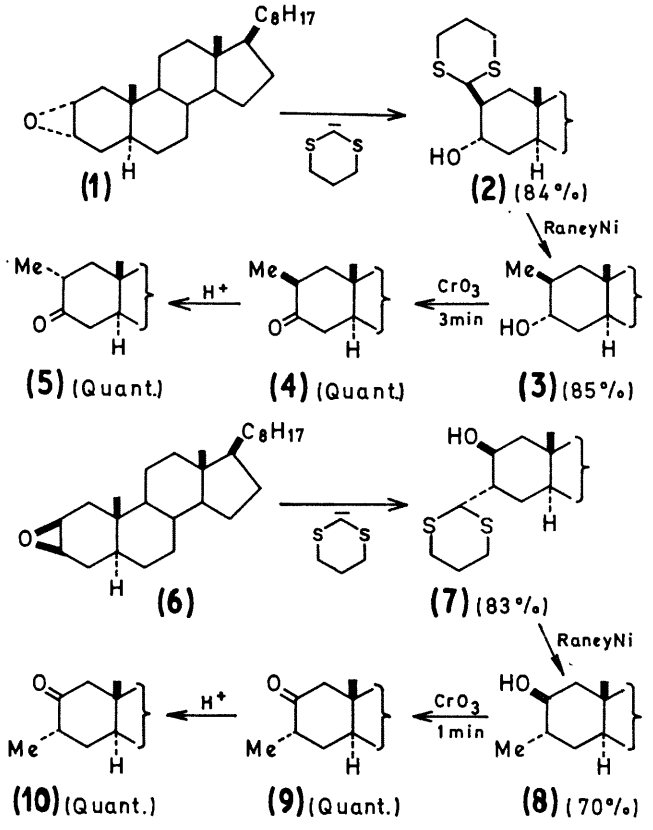
Summary The potential of 2-lithio-1,3-dithian–epoxide reactions for the stereospecific substitution of the steroid skeleton in a desired position has been illustrated by their application in the preparation of both epimers of 2-methyl-3-oxo- and 3-methyl-2-oxo-5α-cholestane.

IN connection with active centre "mapping" and inhibition studies on some enzymes of steroid metabolism stereospecifically substituted steroids were required, including derivatives with α- and β-oriented alkyl groups on the carbon atom adjacent to a ring-A carbonyl group. Although satisfactory methods are available for the preparation of some of the latter compounds, particularly those leading to the thermodynamically preferred derivatives, few routes to the corresponding compounds with the alkyl substituent in the less stable orientation have been described.[1,2] We therefore became interested in developing additional routes to oxo-steroids bearing a substituent on the carbon atom adjacent to the carbonyl group. Attention was concentrated on methods leading first to the thermodynamically less favoured derivative, since such oxo-steroids would be expected to be readily isomerized by acid or base and access to both of the required epimers would then be provided by a single synthetic sequence.

In this regard the reactions of 2-lithio-1,3-dithian[3] with epoxides[4] appeared to be potentially useful in that the analogous reactions of oxiran derivatives of the rigid steroid skeleton should give the stereospecifically substituted hydroxy-precursors required for the preparations of

oxo-steroids alkylated in the thermodynamically less preferred axial positions and the validity of this approach has now been confirmed by the preparations of the methylcholestanones (**4**), (**5**), (**9**), and (**10**) (Scheme).



SCHEME

5α-Cholestane 2α,3α-oxide (**1**)[5] was treated with 2-lithio-1,3-dithian in dry tetrahydrofuran solution at 0° for one week to give the 2β-dithianyl-3α-hydroxy-derivative (**2**). Desulphurisation of (**2**) with Raney nickel in ethanol afforded 2β-methyl-5α-cholestan-3α-ol (**3**) which on oxidation for 3 min. at 0° with Jones' reagent yielded 2β-methyl-5α-cholestan-3-one (**4**) m.p. 97·5—98·5° (lit.[1] m.p. 96—97°). The 2β-axial methyl compound (**4**) was readily epimerized with 20% ethanolic sulphuric acid to give the preferred 2α-methyl epimer (**5**) m.p. 118—120° (lit.[1] m.p. 119—120°).

Reaction of 5α-cholestane 2β,3β-oxide (**6**)[6] with the dithian anion in dry tetrahydrofuran at 0° for two days afforded the 3α-dithianylcholestan-2β-ol (**7**). Raney nickel desulphurisation of (**7**) yielded 3α-methyl-5α-cholestan-2β-ol (**8**) which was then oxidized with Jones' reagent for 1 min. at 0° to give 3α-methyl-5α-cholestan-2-one (**9**) m.p. 128° (lit.[2] m.p. 127—128°). Again, ready epimerization of the axial 3α-methyl group of (**9**) with 10% ethanolic sulphuric acid occurred to give 3β-methyl-5α-cholestan-2-one (**10**) m.p. 150—151° (lit.[7] m.p. 151—153°).

It is of interest to contrast the lithiodithian–epoxide reactions described above and previously[4] with those of similar oxirans with Grignard reagents such as methylmagnesium iodide. For the latter, ring-contraction reactions appear to predominate and treatment of (**6**) with methylmagnesium iodide has been reported to yield 2α-(1′-hydroxyethyl)-A-nor-5α-cholestane in 80% yield with none of the hydroxy-methyl compound (**8**) being isolated.[8]

The ease with which the reactions proceeded, and the excellent yields obtained at every stage, show that lithiodithian–epoxide routes are potentially very useful for the synthesis of a variety of stereospecifically substituted steroids.

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† Satisfactory elemental analyses were obtained for each new compound and the spectral data for all compounds were in accord with the structural and configurational assignments made.

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[2] V. Dovinola and L. Mangoni, *Gazzetta*, 1969, **99**, 206
[3] E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1965, **4**, 1075.
[4] E. J. Corey and D. Crousie, *J. Org. Chem.*, 1968, **33**, 298.
[5] A. Fürst and P. Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.
[6] E. J. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 4832.
[7] L. Mangoni and V. Dovinola, *Chimica e Industria*, 1967, **49**, 166. Other 3-methylcholestan-2-one preparations have been reported previously but from the physical data quoted the samples obtained appear to have been mixtures of (**9**) and (**10**); see F. Biellmann and P. Witz, *Bull. Soc. chim. France*, 1964, 737; B. Cocton and A. Crastes de Paulet, *ibid.*, 1966, 2947.
[8] P. N. Rao and J. C. Uroda, *Tetrahedron Letters*, 1964, 1117.