A New Approach to the Introduction of Corticoid-like C-17 Functions *via* 2-Lithio-1,3-dithian–Epoxide Reactions

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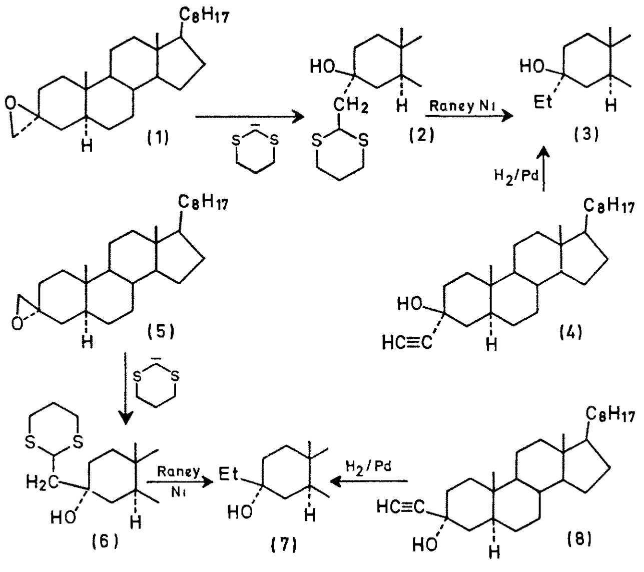
Summary The reactions of the 2-methyl-1,3-dithian anion with the 17α- and 17β-epimers of 3,3'-ethylenedioxy-17-oxiranylandrost-5-ene have been used to illustrate the potential of dithian–epoxide reactions for the introduction of homocorticoid and homoprogestogen types of functions at C-17 of the steroid skeleton.

OUR studies on the potential of 2-lithio-1,3-dithian–epoxide reactions for the stereospecific introduction of desired functions into the steroid skeleton[1] have now been extended to include the reactions of spiro-epoxides.

That such epoxides did react readily to give the desired products which retained their stereochemical integrity was established using the epimeric 5α-cholestanyloxirans (**1**) and (**5**)[2] as being representative of the general types of spiro-epoxides in which we were interested (Scheme 1). On treatment with 2-lithio-1,3-dithian[3] in tetrahydrofuran at 0° for two days they afforded the hydroxydithianyl compounds (**2**) (86% yield) and (**6**) (85%) respectively† which were then desulphurised with Raney nickel to give the corresponding epimeric hydroxyethyl-5α-cholestanes (**3**) (88%) m.p. 137—138° and (**7**) (92%) m.p. 108—109°. The assigned stereochemistries at C-3 of these compounds, and hence of their dithianyl precursors, were confirmed by their unambiguous preparation by hydrogenation of the ethynylcholestanes of established C-3 configurations (**4**) and (**8**).[4] [The above results also inadvertently established that the only 3-ethyl-5α-cholestan-3-ol (m.p. 139°) reported previously[5] had the same C-3 configuration as (**3**).]

In view of the excellent yields obtained and the ease with which the reactions proceeded we investigated the application of the method for the introduction of corticoid-like moieties at C-17 of the steroid nucleus as outlined in Scheme 2.



SCHEME 1

3,3'-Ethylenedioxyandrost-5-en-17-one (**9**)[6,7] was converted into the 17β-oxiran (**10**) m.p. 185–190°[7] in 97% yield with dimethylsulphonium-methylide.[8] The epoxide (**10**) reacted smoothly with 2-methyl-1,3-dithian anion[3] in tetrahydrofuran to give the 17β-hydroxydithianyl product

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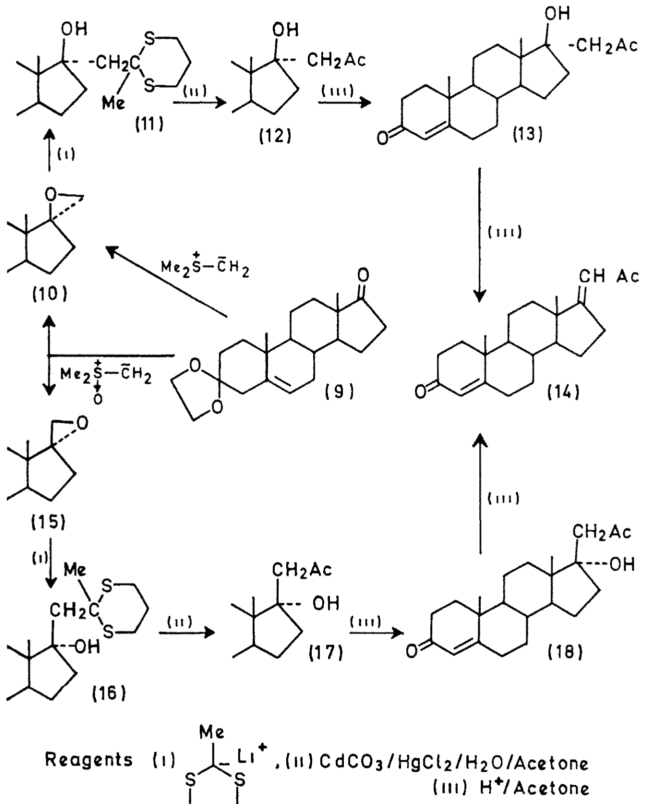
† Satisfactory elemental analyses were obtained for each new compound reported and the spectral data for all compounds were in accord with the structural and configurational assignments shown. Preparative layer chromatography (p.l.c.) was used extensively in product purification.

(11) (68%) m p 164—165° which on treatment with mercury(II) chloride–cadmium carbonate in aqueous acetone[9] yielded **(12)** m p 192—195° in 96% yield Removal of the C-3 acetal group was effected with toluene-*p*-sulphonic acid in acetone at 25° for 4 h to give the Δ^4-3-ketone **(13)** m p 133—134° (78%) which upon more prolonged acid treatment dehydrated smoothly to give 68% of the dienedione **(14)** m p 177—178°



SCHEME 2

The synthetic operations for the corresponding epimeric compounds derived from the 17α-oxiran **(15)** were less readily carried out since treatment of **(9)** with dimethylsulphoxonium-methylide[8] gave in 96% overall yield, a mixture of the epimeric epoxides (10) (68%) and **(15)** (28%) which could not be resolved ‡ However, the corresponding 17-hydroxydithianyl epimers obtained following treatment of the mixture with 2-methyl-1,3-dithian anion were separable by p l c and pure samples of **(11)**, m p and mixed m p 164—165°, and **(16)** were obtained in yields (based on the proportion of each epoxide present) of 68 and 62% respectively Although obtained pure, the 17α-hydroxy-product **(16)** could not be crystallized since it was much less stable than its corresponding 17β-epimer the greater sensitivity of the 17α-series of compounds proved to be a general phenomenon Nevertheless conversion of **(16)** into **(17)** m p 163—166° proceeded in good (58%) yield and the subsequent deacetalisation to the 17α-hydroxyhomoprogesterone **(18)** m p 125—127° was also successful The latter compound was isolated in 34% yield only because of the ease with which it dehydrated to **(14)** (36%), m p and mixed m p 177—178°, under the reaction conditions (catalytic toluene-*p*-sulphonic acid in acetone at 25° for 2 h) necessary to effect complete removal of the C-3 protecting group The contrast between the ease with which **(13)** and **(18)** dehydrate§ again illustrates the relative instability of the 17α-series

The results obtained demonstrate clearly that the above approach constitutes a ready and convenient method for the stereospecific introduction of "homocorticoid" moieties at C-17 of appropriate steroids Further, the C-17 function of **(14)** is reminiscent of those in intermediates in several total or partial syntheses of corticoids[12] which were subsequently elaborated into the desired 17α 20-dihydroxy-20-one function

Financial support from the National Research Council of Canada and the award (to R G) of a University of Toronto School of Graduate Studies Postdoctoral Fellowship are acknowledged

(*Received, April 24th,* 1970 *Com* 603)

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‡ The proportions of each epoxide present were calculated from the relative intensities of the C 18 methyl peaks of **(10)** and **(15)** at δ 0 90 and 0 84 p p m respectively The C 17 stereochemistries assigned to **(10)** (ref 7) and **(15)** were confirmed by comparisons of the ^{1}H n m r spectra with those of the closely similar C-17 spiro epoxides of 5α androstane (ref 7) and 3β hydroxyandrost 5 ene (ref 10) for which chemical verification of the C-17 geometry had been carried out (refs 7 and 10) Further corroboration was provided by a comparison of the pure compounds **(11)**—**(13)** and **(16)**—**(18)** obtained from the epoxide mixture with the authentic samples of **(11)**, **(12)** and **(13)** obtained from pure 17β epoxide **(10)** prepared by the dimethylsulphonium-methylide route

§ If the dehydration of **(13)** and **(18)** to **(14)** occurs *via* a *trans* antiparallel mechanism, examinations of molecular models predict that formation of an E configuration (ref 11) 17 20 double bond is favoured

[1] J B Jones and R Grayshan *Chem Comm* 1970 141

[2] Oxirans (1) and (5) were prepared by the method of C E Cook R C Corley, and M E Wall *J Org Chem* , 1968, **33**, 2789 The criteria of purity used included those quoted by B N Blackett, J M Coxon M P Hartshorn B L J Jackson, and C N Muir, *Tetrahedron* 1969 **25** 1479

[3] E J Corey and D Seebach *Angew Chem Internat Edn* , 1965 **4** 1075

[4] A M Giraud, A Rassat, P Witz and G Ourisson, *Bull Soc chim France* 1964 **31**, 3240

[5] N A Milas and C P Priesing *J Amer Chem Soc* , 1958 **80**, 2189

[6] H J Dauben, B Loken, and H J Ringold, *J Amer Chem Soc* , 1954 **76**, 1359

[7] J D Leman Ph D Thesis University of Toronto 1969

[8] E J Corey and M Chaykovsky, *J Amer Chem Soc* , 1962 **84** 3782, 1965 **87**, 1353

[9] N Pappas and H R Nace *J Amer Chem Soc* 1959 **81**, 4556, M L Wolfrom *ibid* , 1929 **51**, 2188

[10] D Bertin and L Nedelec *Bull Soc chim France* 1964 **31** 2140 The epimeric C-17 epoxides described in this paper also provide attractive starting materials for the types of reactions exemplified in Scheme 2

[11] J E Blackwood, C L Gladys, K L Loening A E Petrarca, and J E Rush *J Amer Chem Soc* , 1968, **90**, 509

[12] L F Fieser and M Fieser Steroids ' Reinhold New York, 1959 ch 19