cis-BC Ring Fusion upon (*E*)-Polyene Cyclizations

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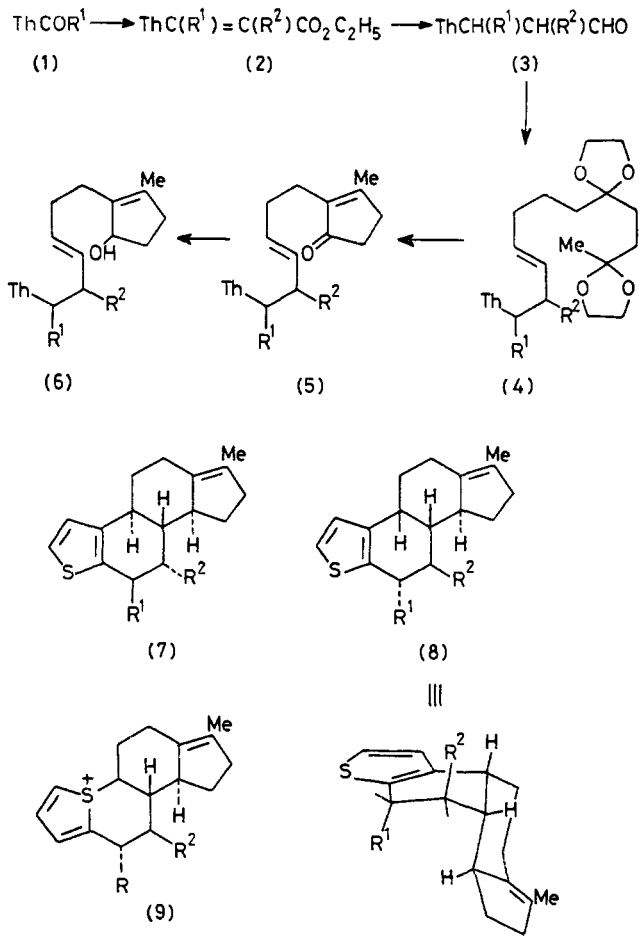
Summary Steroids containing the thiophen unit with *cis*-BC ring fusion are accessible *via* cyclization of (*E*)-polyenes, substituted at pro-C-7 or at pro-C-6 and pro-C-7 (*threo*).†

HETEROCYCLIC 'oestrogen-like' steroids are accessible *via* biomimetic polyene cyclizations.[1] A high diastereomeric preference can be established by asymmetric induction of substituents at pro-C-6.[2]† We report here that a small amount of the steroid mixture, formed upon cyclization of a pro-C-7 substituted (*E*)-polyene, consisted of *cis*-fused tetracycle (16%), When pro-C-6 and pro-C-7 are substituted in a *threo* fashion, the amount of *cis*-fused product is increased (50%).

Only little is known about polyene cyclizations leading to *cis*-fused rings. Generally, a (*Z*)-polyene can lead to *cis*-fused rings (*trans*-fusion only by de- and re-protonation),

† The prefix 'pro' refers to steroid numbering after cyclization. This was first introduced by W. S. Johnson, *J. Amer. Chem. Soc.*, 1976, **98**, 1038. The steroid numbering is according to the I.U.P.A.C. recommendations.

while unsubstituted (*E*)-polyenes provide *trans*-fused rings exclusively. Likewise, the (*E*)-precursor (**6**) ($R^1=R^2=H$) reacts to give the pure *trans*-fused racemic tetracycle (**7**), while its (*Z*)-isomer does not cyclize under a variety of conditions. Earlier studies showed that a relatively small substituent at pro-C-6 (R^1=Me) already generates a high stereospecificity in favour of the 6α-isomer, owing to non-bonded 1,3-diaxial interactions in the precoiled conformer between R^1 and the protons at pro-C-8 and pro-C-10.[2] Model studies showed that a substituent at pro-C-7 undergoes interactions comparable to those of the pro-C-6 precursor and also steric hindrance from the cyclopentenyl nucleus before cyclization.



SCHEME. For all compounds: **a**, R^1 = Me, R^2 = H; **b**, R^1 = H, R^2 = Me; **c**, R^1 = R^2 = Me, *threo*; **d**, R^1 = R^2 = Me, *erythro*. The enantiomers are not drawn. Th = 2-thienyl.

To study these effects in more detail, compounds (**6b—d**) were prepared according to the Scheme.‡ Reaction of (**1**) with triethyl phosphonoacetate or -α-propionate (Wadsworth–Emmons) gave (**2**) as a mixture of the (*Z*)- and (*E*)-isomers. The isomers of (**2c**) were separated by preparative gas chromatography (Apiezone; 196 °C) to yield after hydrogenation the corresponding *erythro* and *threo* derivatives. Hydrogenation of (**2**) followed by reduction with $LiAlH_4$ and oxidation with pyridinium chlorochromate[3] afforded (**3**). These aldehydes underwent a Wittig condensation[4] under Schlosser conditions[5] to yield the (*E*)-alkenes (**4**). Acid treatment effected deacetalisation and subsequent cyclodehydration of the diketones by base afforded the unsaturated cyclopentenones (**5**). The unsaturated alcohols (**6**) were formed on reduction with $LiAlH_4$ and were immediately used for the cyclization experiments. The cyclizations were performed with 1·2 mol equiv. of $SnCl_4$ in CH_2Cl_2 at −95 °C and with 4·3 mol. equiv. of $ZnCl_2$ in $EtNO_2$ at −23 °C. The inseparable steroid mixtures obtained after aqueous work-up with saturated NH_4Cl, were purified by layer chromatography and their composition determined by g.l.c.–mass spectroscopy. ^{13}C-N.m.r. spectra were obtained for the steroid mixtures. The peaks of one set of each mixture (selected by means of relative magnitudes) were found in the same general areas as those for (**7a**)[2] and several other unsubstituted skeletons.[1] A C-7α methyl substituent causes a downfield shift of C-1 of +0·37 p.p.m., comparable to + 0·54 p.p.m. in 7α-methyloestrone methyl ether. Furthermore, a C-7β methyl group in the latter caused an upfield shift of −2·61 p.p.m. at C-1 and −1·33 p.p.m. at C-11, while a *cis*-BC ring fusion causes a downfield shift of 1·03 p.p.m. at C-1. In the second set of the first mentioned mixture an appreciable downfield shift of C-1 (+2 to +3 p.p.m.) was observed, which can only be caused by the loss of a *gauche* 1,4- and/or the gain of a 1,5-interaction between C-1 and C-11 or C-12, respectively, in the *cis*-fused tetracycles (**8**).

The cyclization of (**6a**) at −95 °C, in which only the 1,3-diaxial interactions occur in the precoiled conformer, gave 97% epimerically pure (**7a**) (6α-Me) in 50% yield. However, (**6b**) gave 90% (**7b**) and 10% (**8b**) (also in 50% yield). Compounds (**6c**) and (**6d**) did not give any tetracyclic product under the above mentioned conditions. Therefore, we repeated the experiments at higher temperatures (*vide supra*). The cyclizations of (**6b—d**) each gave a total yield of 34%. Compound (**6b**) gave 84% (**7b**) and 16% (**8b**). Surprisingly, (**6c**) provided 40% (**7c**) and 50% (**8c**). The influence of R^1 increases *cis*-fusion owing to additional 1,3-interactions before cyclization. Two minor compounds (each 5%) were also formed and can be ascribed to double-bond isomerized products. The structures formed upon cyclization of (**6d**) could not be elucidated owing to polymerization, as was evident from ^{13}C-n.m.r. and mass spectroscopy.

During the course of this work we were informed[6] that the cyclizations of pro-C-7 substituted alkenes with anisole as pro-A-ring lead to 7α and 7β substituted pure *trans-anti*-fused tetracycles. These structures were firmly established by comparison with naturally derived products. We could then study the spectroscopic properties of a number of natural C-7 substituted, *cis*- or *trans*-fused steroids§ (*vide supra*). Since the seemingly equal cyclization experiments

‡ All the products were racemic.

§ These compounds were kindly made available by Organon SDG, which we gratefully acknowledge.

lead to different results we must conclude that compounds (**8**) are formed *via* the intermediacy of the ion (**9**).

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