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SYNTHESIS OF A CYCLIC SULPHONAMIDO PROSTAGLANDIN ANALOGUE

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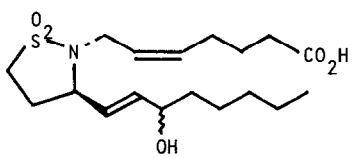
Summary Ethyl 8-nonenoate was converted into a new heterocyclic (sultam) prostanoid by a simple procedure involving photocatalysed addition of *N*-bromo-*N*-methylmethanesulphonamide to the olefin and cyclization of the adduct to a sultam, which was formylated and ketovinylated to provide two methods of introducing the β-side chain.

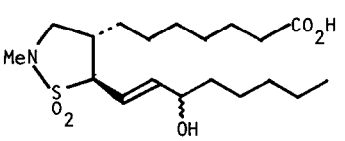
The *S,N*-heterocyclic prostaglandin analogues which have been synthesized[1-4] in the quest for compounds of specific biological activity are, in the majority, thiazole[1] or thiazolidinone derivatives.[2] The sole cyclic sulphonamide (sultam) example (1) displayed marked activity in stimulating formation of cAMP,[4] and acyclic sulphonamido prostanoids showed activity of significant potency and selectivity.[5] This information prompted us to synthesize the new sultam prostanoids (2), by procedures which are capable of general application.

Irradiation of a solution of ethyl 8-nonenoate and *N*-bromo-*N*-methylmethanesulphonamide in dry benzene (20 °C, 1 h, using a medium pressure mercury lamp) gave the adduct (3) (55%),[6,7] which on reduction to (4) ($LiAlH_4$, ether, 0 °C) and subsequent protection of the hydroxy group gave the sulphonamide derivative (5) [71% from (3)]. Cyclization of (5) to (7) proceeded in 82% yield on treatment with butyl-lithium (1 equiv.) in THF at -20 °C for 4.5 h.[6] The acid (6) obtained by hydrolysis of (3) (86%) also cyclized under similar conditions (using two equiv. of butyl-lithium) to give (8) (68%).

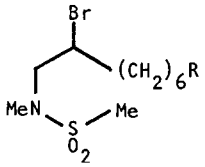
Treatment of the sultam (7) in THF at -78 °C in sequence with butyl-lithium (1.1 equiv. for 1.25 h) and ethyl formate (1.5 equiv. for 3 h) gave the formyl derivative (9) (87%),[8] which existed in tautomeric equilibrium with its hydroxymethylene form (60% of the mixture) according to NMR spectroscopy. The presence of one discrete aldehyde signal (δ 9.70, d, J 2 Hz) indicated that only one aldehyde epimer was present: this was reasonably assumed to be the trans isomer (9). Wittig olefination using 1-tributylphosphoranylidene-2-heptanone[9] (ether, 20 °C, 16 h) gave the (E)-enone (10) (79%) together with its (Z)-isomer (2%), which were separated by chromatography (silica, ether-petroleum ether, 2:3). In an alternative stereospecific procedure the sultam (7) was treated in sequence with butyl-lithium (1.1 equiv.) and 2-phenylsulphinyloct-1-en-3-one[10] (1 equiv.) in THF at -78 °C for 3 h to give the adduct



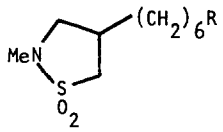
(1)



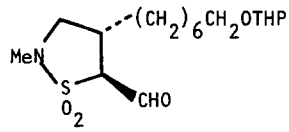
(2) a, 15α-OH
b, 15β-OH



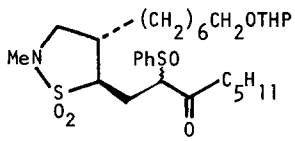
(3) R = CO_2Et
(4) R = CH_2OH
(5) R = CH_2OTHP
(6) R = CO_2H



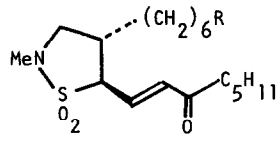
(7) R = CH_2OTHP
(8) R = CO_2H



(9)



(13)



(10) R = CH_2OTHP
(11) R = CH_2OH
(12) R = CO_2H

(13) (79%), which on thermolysis in boiling toluene containing trimethyl phosphite for 30 min. gave the pure (E)-enone (10) (50%). Acylation and alkylation of the dianion derived from the acid (8) was frustrated by its poor solubility in a variety of solvent systems.

Deprotection of (10) to give the alcohol (11) (86%) followed by Jones oxidation to the acid (12) (85%) and subsequent reduction with sodium borohydride in ethanol gave a mixture (92%) of the 15-alcohols (2a) and (2b), from which pure samples of the epimers was obtained by esterification with diazomethane, HPLC separation (14μ silica, di-isopropyl ether) and subsequent saponification. The compounds (2a) and (2b) were weak antagonists of PGE_2 and $PGF_{2\alpha}$ on various smooth muscle preparations. They exhibited no significant effect upon blood platelet aggregation.

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References and note

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