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SYNTHESIS OF ANALOGS OF PROSTACYCLIN CONTAINING A THIAZOLE RING[1]

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Summary: Thiazole analogs of prostacyclin were prepared from the cyclopentene (9), itself obtained via a novel opening of 3,4-epoxycyclopentene with the lithioallylthioether (4).

Widespread interest in the synthesis and biological properties of prostacyclin (PGI_2, (1))[3] has followed the discovery that prostacyclin both inhibits platelet aggregation and induces vasodilation.[4] However, therapeutic use of prostacyclin is precluded by its rapid hydrolysis to 6-oxo-$PGF_{1\alpha}$,[5] and consequently a wide range of stable analogs of prostacyclin has been prepared.[3,6] Of these the only reported "heteroaromatic" prostacyclins are pyrazoloprostacyclin,[6f] and 6,9-pyridazaprostacyclin,[6b] for which significant biological activity has been claimed.

This communication describes the synthesis of analogs (18), (20) and (25) and the corresponding methyl esters, in which the tetrahydrofuran ring of (1) is formally replaced by a thiazole nucleus. It was envisaged[7] that these and other heterocyclic prostacyclin analogs would be available from an intermediate such as (9) following selective functionalization of the cyclopentene double bond. A compound of this type was used in a synthesis of prostaglandin $F_{2\alpha}$, with hypobromite addition having been found to occur selectively in the desired fashion.[8]

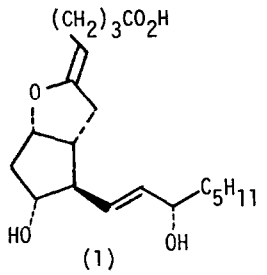
Two routes to the new diol (9) were employed, both commencing with 1,2-opening of 3,4-epoxycyclopentene (2) by a carbanion. Reaction of (2)[9] with the lithium acetylide (3) under the published conditions gave the known cyclopentenol (5)[8] as the major product (29% after chromatography). De-protection of (5) (p-TsOH/MeOH/25°) and reduction of the resulting acetylenic diol (6)[10] (3 equiv. $LiAlH_4$/THF/reflux) then provided (9) (82% from (5)). The poor yield of epoxide opening in this sequence prompted development of a superior route to the diol (9). Cleavage of (2) (1.2 equiv) with the lithiated pyridyl allyl thioether (4) (THF/-78°) gave the cyclopentenol (7) (62% after chromatography) as a 1:1 mixture of epimers at the carbon atom α to sulfur. Products from 1,4-opening of the epoxide or γ-attack on the thioallyl anion were not evident in significant amounts. While quenching of thioallyl anions has been widely used with a variety of electrophiles, including alkyl halides,[11] ketones[12] and enones,[13] no examples of their reaction with epoxides appear to have been reported. Oxidation of (7) (1 equiv. m-CPBA/CH_2Cl_2/-78°) followed by rearrangement[11] of the resulting crude allyl sulfoxide (8) in trimethyl phosphite afforded (9) (71% from (7)), identical in all respects with material from the previous route.

The diol (9) was protected as the bisbenzyloxymethyl ether (10) (4 equiv. $PhCH_2OCH_2Cl/Pr_2NEt/25^0$, 77%), since it had been reported[8] that this protecting group was of significance in hindering electrophilic attack on the side chain double bond.[14] Treatment of (10) with N-bromosuccinimide (1.5 equiv.) in aqueous DMSO[8] gave a mixture of two readily separable bromohydrins, to which the structures (11) (57%) and (12) (12%) were assigned on the basis of their ^1H nmr spectra. In each isomer the orientation of addition follows from D_2O exchange of the hydroxyl proton and de-coupling experiments, while the stereochemistry of addition is inferred from the chemical shifts of the protons at C-10 and C-12 (prostaglandin numbering)[15] and is opposite to that assigned previously to an analogous known compound[8]. Oxidation of the major bromohydrin (11) (4 equiv. pyridinium chlorochromate[16]/CH_2Cl_2) gave the bromoketone (13) (94%) as a mixture of epimers at C-8.

Reaction of (13) with the thioamide (14) (obtained by treatment of methyl adipamate with phosphorus pentasulfide) under standard conditions[17] failed to give the expected thiazole (20). Heating (13) and (14) together in dioxan, acetone or methanol caused both considerable decomposition and formation of several products. A much cleaner reaction ensued from mixing the two components in the absence of solvent at room temperature to form the hydroxythiazoline (15).[18] Although dehydration of (15) was not accomplished by a variety of standard reagents, treatment of crude (15) with 6 equiv. of the complex of triphenyl phosphine and diethyl azodicarboxylate[19] (THF/25^0) resulted in clean elimination to the desired thiazole (16) (67% from (13)). De-protection of (16) was effected (52%) with p-toluenesulfonic acid (3 equiv.) in methanol at 25^0 over 10 days. Finally hydrolysis (NaOH/aq. MeOH/25^0) of the resulting diol ester (17) afforded the prostacyclin analog (18), together with its 15-epimer (19).[20] Neither this mixture of epimers nor the mixtures obtained for the preceding compounds subsequent to the diol (9) were readily separable by chromatographic means. Similarly the nor-prostacyclin analog (20) and its 15-epimer (21) were prepared starting from the bromoketone (13) and the thioamide derived from methyl glutaramate.

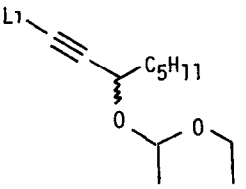
Heating the crude hydroxythiazoline (15) in methanol at 50^0 caused solvolysis to the methoxythiazoline (22) (62% from (13)) as a ca 2:1 mixture of cis and trans ring-junction isomers. De-protection produced a mixture of diol-esters, which could be separated into the individual 15-epimers (23) and (24), although the ring-junction isomers remained inseparable. Thus (23) and (24) were isolated and hydrolysed to the corresponding acids (25) and (26).

When tested *in vitro* for inhibition of ADP induced platelet aggregation[21] most of these analogs showed weak to moderate biological activity, with the methoxy derivative (25) being the most potent (0.16 x PGE_1). This observation may imply that for maximum activity in compounds of this type the α-cis ring-junction present in prostacyclin should be retained. It is also noteworthy that whereas compound (18)[22] displayed activity (0.07 x PGE_1), the nor-analog (20)[22] was inactive at concentrations up to 10^{-4} M.

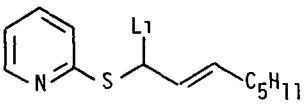


(1)

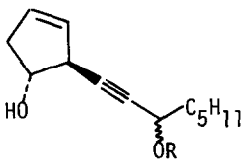
(2)



(3)

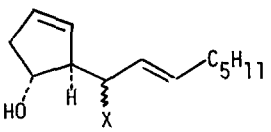


(4)



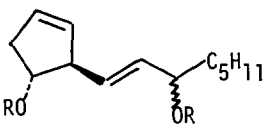
(5) R = CH_3CHOEt

(6) R = H



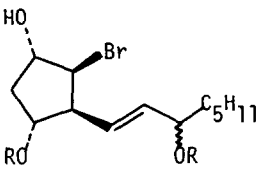
(7) X = 2-PyS-

(8) X = 2-PyS(=O)

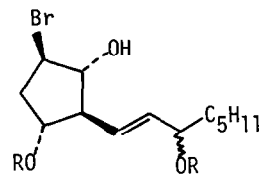


(9) R = H

(10) R = $PhCH_2OCH_2$



(11)



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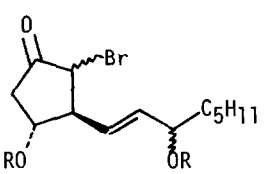

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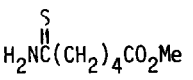
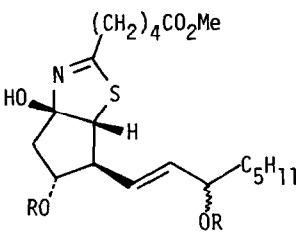
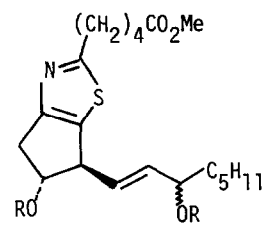


(14)

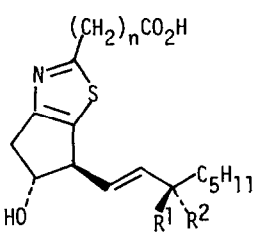


(15)



(16) R = $PhCH_2OCH_2$

(17) R = H

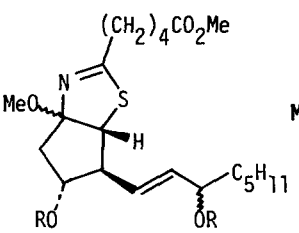


(18) n=4, R^1 = H, R^2 = OH

(19) n=4, R^1 = OH, R^2 = H

(20) n=3, R^1 = H, R^2 = OH

(21) n=3, R^1 = OH, R^2 = H



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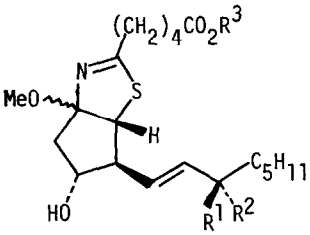

(23) R^1 = H, R^2 = OH, R^3 = Me

(24) R^1 = OH, R^2 = H, R^3 = Me

(25) R^1 = H, R^2 = OH, R^3 = H

(26) R^1 = OH, R^2 = H, R^3 = H

Compounds (11), (12), (13), (15), (22) R = $PhCH_2OCH_2$

References and Notes

1. Contribution No. 621 from the Institute of Organic Chemistry.
2. Syntex postdoctoral fellow, 1980-81. Present address: Chemistry Department, ICI Ltd., Pharmaceuticals Division, Mereside Alderley Park, Macclesfield, Cheshire, England.
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18. Spectral data for purified (18)·νmax (film) 3200, 1725, 1600 cm^{-1}; δ ($CDCl_3$), 0.88 (3H, t), 1.2-1.7 (12H, m), 2.03 (1H, dd, J 10, 15 Hz), 2.3-2.55 (5H, m), 2.76 (1H, dd, J 6, 15 Hz), 3.48, 3.52 (1H, ratio 1:1, both s, J 9 Hz),4.03 (2H, m), 4.5 - 4.8 (8H, m), 5.48 (1H, dd, J 7, 16 Hz), 5.66 (1H, m), 7.30 (10H, m); m/e (C.I.) 622(MH^+-H_2O), 560, 502, 434, 364, 279.
19. For a review on the uses of this reagent see: O. Mitsunobu, Synthesis, 1981, 1.
20. Spectral data for mixture of (2) and (22). $\delta(CDCl_3)$, 0.88 (3H, t), 1.2-1.9 (12H, m), 2.39 (2H, t), 2.78 (1H, dd, J 4, 15, Hz), 3.00 (2H, t), 3.25 (1H, m), 3.70 (1H, m) 4.12 (1H, m), 4.58 (1H, m), 5.70 (2H, m);m/e 367 (M^+), 349, 296, 278.
21. We thank Dr. J. Bruno, Institute of Biological Sciences, Syntex Research, for performing this assay.
22. Tested as a 1:1 mixture with the corresponding 15-epimer.

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