Synthesis of Sulphur-containing Prostacyclin PGI_1 Analogues 6,9-Epithio-PGI_1, its *S*-Oxide Stereoisomers, and its *SS*-Dioxide

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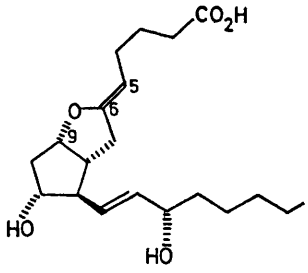
Summary The synthesis of the biologically active PGI_1 analogues, 6,9-epithio-PGI_1, its *S*-oxide stereoisomers, and its *SS*-dioxide is reported.

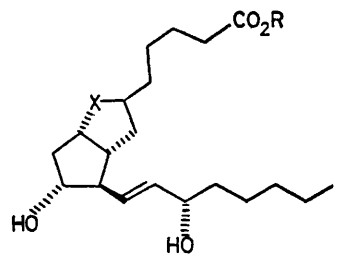
THE important physiological role and the therapeutically promising properties of prostacyclin (PGI_2)[1,2] (**1**), coupled with its rather unstable nature, make the design and synthesis of stable biological mimics of this molecule highly desirable. In this communication we report the synthesis of a number of sulphur-containing[3] 5,6-dihydroprostacyclins, namely 6,9-epithio-5,6-dihydroprostacyclin (**2c**), and its *S*-oxides (**3c**; sulphoxide stereoisomers) and *SS*-dioxide (**4c**).

A degassed solution of the 9-thio-$PGF_{2\alpha}$ derivative (**7**)[3] in AcOH–tetrahydrofuran(THF)–H_2O (3 : 2 : 2) was heated at 45 °C for 20 h to produce directly the methyl ester (**2a**)†[4] (79%) by removal of the silyl ethers and concurrent acid-catalysed intramolecular ring closure. In order to explore

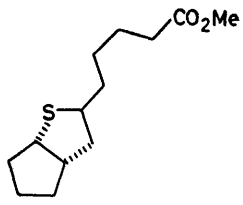
† Satisfactory spectral data were obtained for all new compounds.



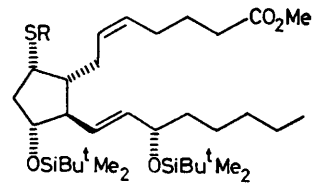
(1)



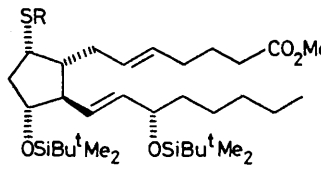
(2) X = S
(3) X = S→O
(4) X = SO_2
a; R = Me, b; R = Na,
c; R = H



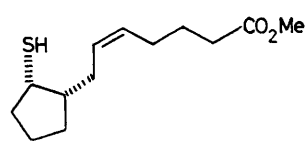
(5)



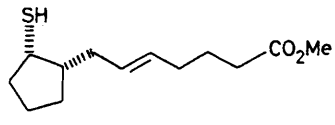
(6); R = Ac
(7); R = H



(8); R = Ac
(9); R = H

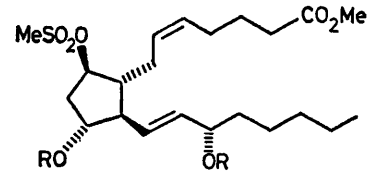


(10)

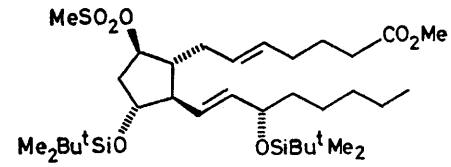


(11)

the possibility of forming the other C-6 epimer of (**2**) the 9-thioacetoxy-*trans*-$PGF_{2\alpha}$ derivative (**8**) was synthesized as follows. The 9β-methylsulphonyloxy-11,15-bis(tetrahydropyranyl)-$PGF_{2\alpha}$ methyl ester (**12**)[3] was converted into the 11,15-bis(t-butyldimethylsilyl) ether (**14**) *via* the diol (**13**) [(i) AcOH–THF–H_2O, 3:2:2, 45 °C; (ii) t-butyldimethylsilyl chloride–imidazole–dimethylformamide, 25 °C] in 90% overall yield. Irradiation of this bis(silyl) ether with u.v. light in the presence of diphenyl disulphide (0·5 mol equiv.) in degassed benzene solution at 20 °C for 4 h afforded an equilibrium mixture of 5(*E*)- and 5(*Z*)-isomers (**15**) and (**14**) with the 5(*E*)-isomer predominating (*ca.* 85:15).[5] Column chromatography on silver nitrate-impregnated silica gel led to isolation of pure (**15**) (80%) and recovery of the starting compound (**14**) (14%). Exposure of (**15**) to an excess of potassium thioacetate in dimethyl



(12); R = Tetrahydropyranyl
(13); R = H
(14); R = $SiBu^tMe_2$



(15)

sulphoxide at 45 °C for 24 h furnished the thioacetate (**8**) (86%). However, when the thiol (**9**) [obtained from (**8**) on exposure to K_2CO_3 in MeOH] was subjected to the cyclization conditions described above, the same 5,6-dihydro-6,9-epithioprostacyclin (**2**) was obtained. This observation suggests the intermediacy of a discrete carbonium ion in this ring closure reaction. The model compounds (**10**)‡ and (**11**)‡ were also found to undergo this easy cyclization under acidic, anaerobic conditions ($MeC_6H_4SO_3H$-*p*, CH_2Cl_2, 25 °C) yielding the cyclic sulphide (**5**) recently reported by Shibasaki and Ikegami.[6] In agreement with these authors,[6] we also observed the instability of the above thiols towards disulphide formation and cyclization to the sulphides on exposure to air and/or silica gel. These compounds were, therefore, freshly generated from their corresponding acetates under basic and strictly anaerobic conditions and used immediately without purification.

Oxidation of (**2a**) with *m*-chloroperbenzoic acid (1·1 mol. equiv., CH_2Cl_2, −78 °C) or H_2O_2 (THF, 25 °C) furnished the *S*-oxide methyl ester (**3c**) as a mixture of sulphoxide stereoisomers (70%) separated by preparative layer chromatography (silica gel, 10% MeOH in CH_2Cl_2) into a major isomer (R_f = 0·26) and a minor isomer (R_f = 0·33) (*ca.* 2:1 ratio).

Exposure of (**2**) to diphenyl diselenide (0·5 mol. equiv.) and hydrogen peroxide[3b] (10 mol. equiv.) in THF at 25 °C for 4 h resulted in the formation of the *SS*-dioxide methyl ester (**4a**) in 93% yield, presumably by the action of PhSe(O)OOH[7] formed *in situ* under these conditions. This new methodology for oxidation of sulphides to sulphones appears to be very promising owing to its selectivity and mildness.

‡ Prepared from cyclopentene oxide as follows: (i) epoxide opening with lithium acetylide–ethylenediamine complex, (ii) protection as t-butyldimethylsilyl ether, (iii) hydroboration–oxidation to the aldehyde, (iv) condensation with the ylide derived from 4-carboxybutyltriphenylphosphonium bromide, (v) deprotection of the alcohol, (vi) mesylation, (vii) displacement with potassium thioacetate, and (viii) deprotection with methoxide in absolute methanol. The *trans*-olefin was obtained by photolytic–Ph_2S_2 isomerization of the *cis*-isomer at the silyl ether stage and purified by silica gel–silver nitrate column chromatography.

In agreement with the 6β-stereochemical assignment to (**5**)[6] and on the basis of ^{1}H n.m.r. spectroscopy we tentatively assign the 6β-configuration to all the above PGI_1 analogues.

Basic hydrolysis of the methyl esters (**2a**), (**3a**), and (**4a**) with 90% EtOH containing NaOEt (5 mol equiv.) produced smoothly the corresponding sodium salts (**2b**)—(**4b**) which could be directly employed for bioassays after suitable dilutions or acidified to yield the acids (**2c**)—(**4c**) after extraction with ether.

Preliminary biological results obtained with (**2a**) indicate weak inhibitory activity in human blood platelet aggregation and vascoconstricting activity in isolated cat coronary artery.

We thank Merck Sharp and Dohme, U.S.A., O.N.O. Pharmaceutical Co., Japan, and the Research Corporation, U.S.A., for financial support. Tests of platelet aggregation were carried out in the laboratories of Professors J. B. Smith and M. J. Silver, The Cardeza Foundation, Thomas Jefferson University, Philadelphia. The effect of (**2a**) on the cat coronary artery was determined by Dr. M. Ogletree and Miss Cherie Ditre in Professor A. M. Lefer's laboratory, Department of Physiology, Thomas Jefferson Medical College, Philadelphia.

(*Received*, 29*th December* 1977; *Com.* 1316.)

[1] S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 663; R. Gryglewski, S. Bunting, S. Moncada, S. Flower, and J. R. Vane, *Prostaglandins*, 1976, **12**, 685; S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane, *ibid.*, 1977, **13**, 3; R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Wittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *ibid.*, 1976, **12**, 915.

[2] For a review, see: K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, *Angew. Chem.*, in the press.

[3] For the synthesis of other sulphur-containing PGI_2 analogues, see: (a) K. C. Nicolaou, W. E. Barnette, G. P. Gasic, and R. L. Magolda, *J. Amer. Chem. Soc.*, 1977, **99**, 7736; (b) K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, *ibid.*, in the press.

[4] See also: M. Shibasaki and S. Ikegami, *Tetrahedron Letters*, 1978, 559.

[5] For examples of recent similar isomerizations in the prostaglandin area, see: E. J. Corey, I. Szekely, and C. S. Shiner, *Tetrahedron Letters*, 1977, 3529; W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Amer. Chem. Soc.*, 1977, **99**, 1222.

[6] M. Shibasaki and S. Ikegami, *Tetrahedron Letters*, 1977, 4037.

[7] P. A. Grieco, Y. Yokoyama, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1977, **42**, 2034; P. A. Grieco, Y. Yokoyama, S. Gilman, and Y. Ohfune, *J.C.S. Chem. Comm.*, 1977, 870; K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, *J. Amer. Chem. Soc.*, in the press.