Simple Efficient Synthesis of Prostacyclin (PGI_2)[1]

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Summary A simple, efficient synthesis of prostacyclin (PGI_2) from the methyl ester of prostaglandin $F_{2\alpha}$ is reported.

AN unstable prostaglandin was recently found to have very potent activity as an inhibitor of the aggregation of human blood platelets and was called prostaglandin X (PGX).[2] This substance is now referred to as prostacyclin or PGI_2 and its structure (I) has been reported[3] and confirmed by synthesis.[4] It is generated by human blood vessels in small amounts from arachidonic acid *via* PGG_2 or PGH_2.[5] Investigations concerning the function of prostacyclin in the blood require an efficient method of preparation from readily available starting materials, and we report here a simple, efficient synthesis of prostacyclin (I) from $PGF_{2\alpha}$ methyl ester (IV).

Our recent synthesis[6] of the stable prostacyclin isomer (III) from $PGF_{2\alpha}$ *via* the phenyl selenide (V) demonstrated the high reactivity of the $PGF_{2\alpha}$ system towards ring closure to form a five-membered ring ether, involving C(6) and C(9)O.[7] We have now investigated the addition of halogens (I_2, Br_2) to $PGF_{2\alpha}$ methyl ester (IV).

Iodine (1·2 equiv.) reacted (24 h) with (IV) in methylene chloride at −10 °C in the presence of potassium carbonate (2 equiv.) to afford a major iodide (VI)† (90%) accompanied by a minor isomer (6%). The two isomers could be separated by preparative t.l.c. [silica gel; acetone–methylene chloride, 30:70; R_f 0·15 (major) and 0·19 (minor)]. The relative stereochemistry of these isomers has not been determined. Either isomer of (VI) or a mixture of the two (10^{-2} M solution) on exposure to: (A) 1,5-diazabicyclo-[5.4.0]undec-5-ene (5 equiv.) in toluene at 110 °C (0·5 h) or (B) sodium methoxide (or ethoxide) (5 equiv.) in absolute methanol (ethanol) at 75 °C (0·5 h) afforded prostacyclin methyl (ethyl) ester (II) in essentially quantitative yield. Removal of the solvent *in vacuo* at ambient temperature, extraction with cold (0 °C) ether, washing twice with pH 5 buffer solution and once with water, followed by drying (K_2CO_3–$MgSO_4$) and evaporation (0 °C) led to pure samples of (II) [R_f (silica gel, 5% methanol in ether) 0·39; i.r. (liquid film) ν_{max} 1733 (ester) and 1675 cm^{-1} (enol ether); *m/e* 366 (M^+); $[\alpha]_D^{22}$ + 66·10° in MeOH]. Stable basic solutions of the sodium salt of prostacyclin (I) in high purity were obtained by procedure (B) by adding 5% water and heating at 75 °C for further 3·5 h to achieve

† Satisfactory spectral data were obtained for all new compounds.

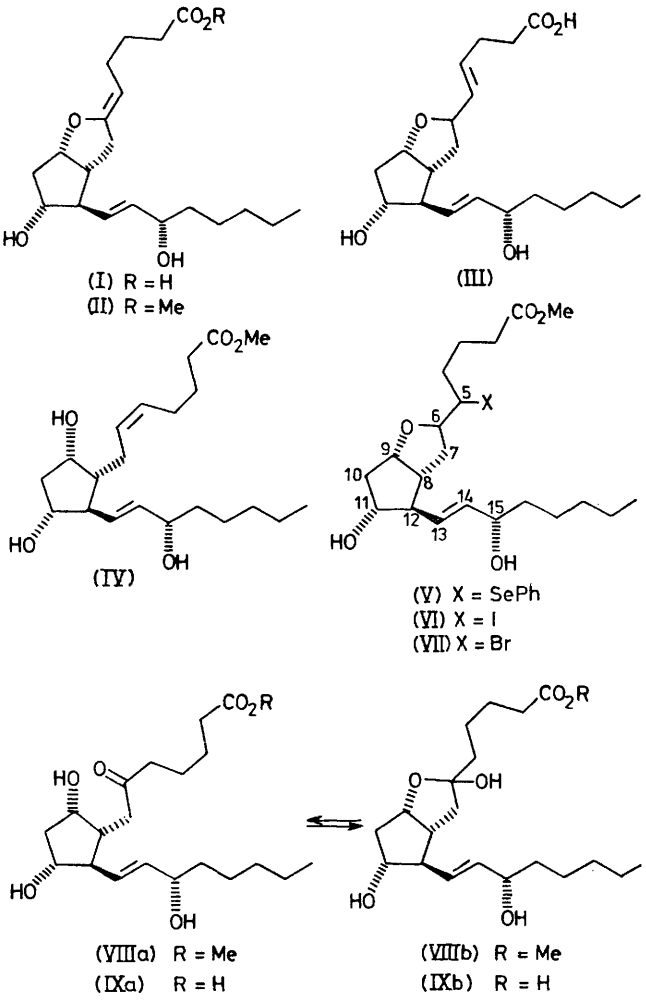
removal of the methyl ester [R_f (silica gel, 5% methanol in ether) 0·10]. These solutions were stable at ambient temperatures for prolonged periods and could be used for bioassays directly after dilution with suitable buffers. The essentially quantitative transformations (VI) → (II) → (I) were directly observed by t.l.c. and n.m.r. spectroscopy; *e.g.* compound (VI), τ (basic CD_3OD) 4·46 (m, 2H, 13- and 14-H), 5·49 (m, 1H, 5-H), and 5·84, 6·00, 6·15, and 6·26 (m, 1H each, 9-, 11-, 15-, and 6-H); compounds (I) and (II) similar, except for absence of signal at τ 6·26. The geometry of the enol ether double bond in (I) and (II) was assigned on mechanistic grounds for the formation and dehydrohalogenation of the intermediate (VI) and was confirmed by the biological properties of (I) and n.m.r. spectroscopy.[4] Prostacyclin (I) can also be prepared *via* the bromoether (VII)[4] by the sequence described above, although the addition of bromine to (IV) affords lower yields of the bromide, and the dehydrohalogenation step requires longer reaction periods.

The prostacyclin methyl ester (II), although reasonably stable in neutral or basic media, rearranges rapidly to 6-oxo $PGF_{1\alpha}$ methyl ester (VIIIa), in equilibrium with its lactol form (VIIIb), under acidic conditions. Prostacyclin (I) itself is stable in basic media at room temperature but shows even higher lability than its methyl ester towards formation of 6-oxo $PGF_{1\alpha}$ (IX), in equilibrium with its lactol form (IXb), under neutral or acidic conditions.

Synthetic prostacyclin showed the expected[2] biological activity as an inhibitor of platelet aggregation using human, rabbit, cat, rat, and guinea pig platelets.[8]‡

We thank Dr. Gabriel Gasic, Department of Pathology, for support and encouragement in the initial part of this work and the University of Pennsylvania for financial support.

(*Received*, 20*th June* 1977; *Com.* 604.)



‡ We thank Professors M. J. Silver and J. B. Smith of the Cardeza Foundation and Department of Pharmacology, Thomas Jefferson University, Philadelphia, Pennsylvania, for carrying out the biological tests. *In vivo* biological studies are being conducted by Professor Alan Lefer, Thomas Jefferson Medical College, Philadelphia; both sets of results will be published elsewhere.

[1] This work was presented in part at the A.C.S. Middle Atlantic Regional Meeting, Newark, Delaware, April, 1977 (Abstracts, Organic Chemistry, paper 21).

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