

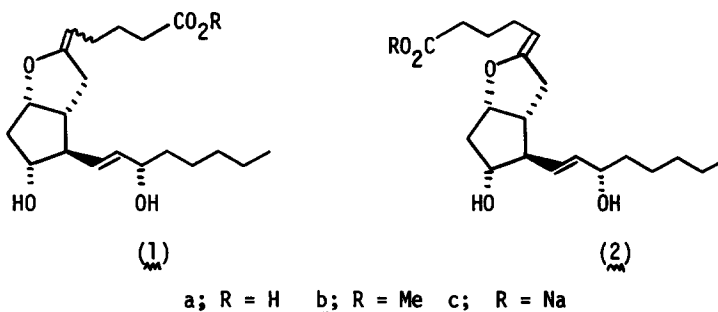
A SYNTHESIS OF PROSTACYCLIN SODIUM SALT

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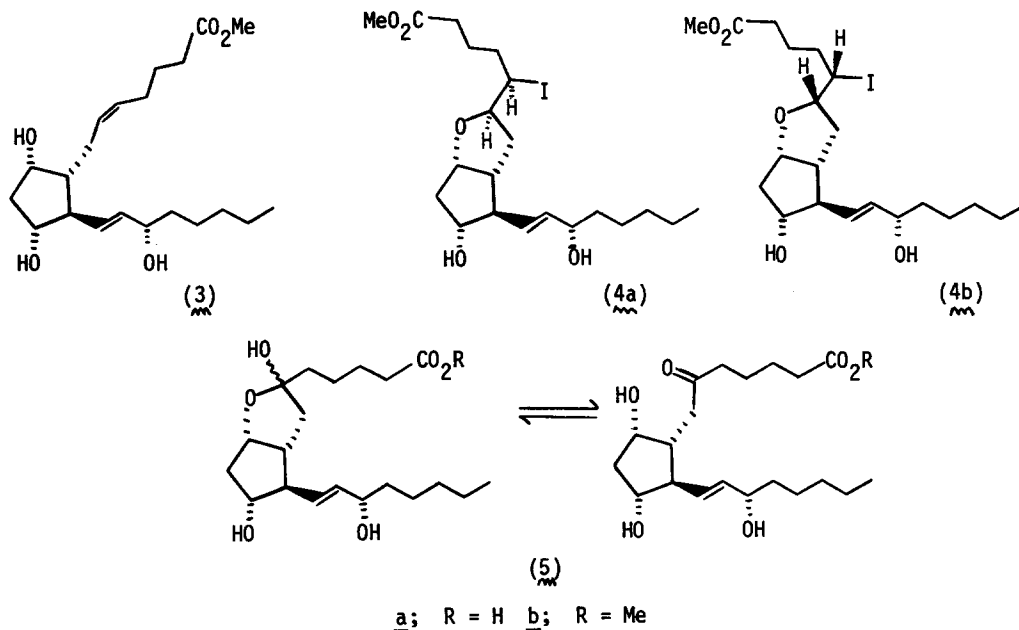
In 1976 a new prostaglandin-endoperoxide metabolite, prostaglandin X (PGX), was isolated<sup>1</sup> and its homeostatic rôle in the regulation of platelet aggregation<sup>2</sup> and some of its pharmacological properties<sup>3</sup> have been described. PGX was shown<sup>4</sup> to be 5,6-didehydro-9-deoxy-6,9 $\alpha$ -epoxyprostaglandin F<sub>1 $\alpha$</sub>  (1a) and was given the trivial name prostacyclin. Johnson and his colleagues<sup>5</sup> have now established by synthesis the (5Z) orientation for prostacyclin, as depicted in formula (2a).



Independently, a methyl ester (1b) and sodium salt (1c) have been synthesised in this laboratory from prostaglandin F<sub>2 $\alpha$</sub>  methyl ester (3) in high yield by a short sequence of reactions carried out at or below room temperature. The identity of this sodium salt with the sodium salt (2c) of prostacyclin follows from the equivalence of their inhibitory action on platelet aggregation and from considerations of the synthetic steps employed.

On the basis of the known<sup>6</sup> reaction of 5-hydroxy-1-alkenes with halogens to give 2-halogenomethyltetrahydrofurans, it seemed likely that PGF<sub>2 $\alpha$</sub>  methyl ester (3) could be converted into the iodo-compound (4a or 4b) since the 9-hydroxy group of (3) is in a sterically favourable (cis) orientation relative to the side chain bearing the 5,6-ethylenic bond. In practice, the desired reaction occurred when 0.7M aqueous KI<sub>3</sub> (1.1 mol. equiv.) was added dropwise during 3 hours to a well-stirred mixture of ethereal PGF<sub>2 $\alpha$</sub>  methyl ester<sup>7</sup> with saturated aqueous NaHCO<sub>3</sub> (10 mol. equiv.) at room temperature. After stirring overnight, aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added, and the ethereal phase was washed (H<sub>2</sub>O) and dried (MgSO<sub>4</sub>); removal of the ether afforded 5 $\xi$ -iodo-

9-deoxy-6 $\epsilon$ ,9 $\alpha$ -epoxyprostaglandin F<sub>1 $\alpha$</sub>  methyl ester (4) (90% yield) as a yellow gum with only trace impurities. The use of 1.1 mol. equiv. of a 2.5% solution of iodine in ether or methylene chloride in a similar 2-phase system at 0° effected a cleaner reaction, yielding (4) almost quantitatively as a pale yellow gum. T.l.c. examination of this product on SiO<sub>2</sub> in two systems (AIX<sup>8</sup>, EtOAc saturated with H<sub>2</sub>O) pointed to it being a single species<sup>9</sup>, a conclusion supported by high resolution <sup>1</sup>H n.m.r. in CDCl<sub>3</sub>, and the configuration (4a) or (4b) is proposed for it. The possibility that the ester (3) had initially undergone isomerisation to the 5,6-*trans*-isomer, and thence exclusively via a different iodonium species to a stereoisomer(s) of (4a) or (4b), was remote since initially the rate of consumption of iodine and formation of product (monitored by t.l.c.) were rapid.



The iodo-ester (4) was smoothly converted by 1,5-diazabicyclo-5-nonene (DBN) in the absence of solvent at room temperature into an acid-labile vinyl ether. Its formation could be followed by t.l.c. (SiO<sub>2</sub>, AIX system)<sup>10</sup> and was complete after a few hours. The DBN and HI were conveniently removed by adsorption on to a column of SiO<sub>2</sub>, prepared from a suspension of SiO<sub>2</sub><sup>11</sup> in EtOAc/Et<sub>3</sub>N 50:1, and the vinyl ether was eluted with the same solvent system. Its formulation as a 5,6-didehydro-compound (5) was established by i.r. spectroscopy [thin film,  $\nu_{\max}$  1738 (CO<sub>2</sub>Me) and 1696 cm<sup>-1</sup> (-O-C=C-)], <sup>1</sup>H n.m.r. in C<sub>6</sub>D<sub>6</sub>-Et<sub>3</sub>N, 19:1 [ $\delta$ 4.22, triplet of triplets<sup>12</sup>, J<sub>6,9</sub> and 1.0 Hz (C-5 vinyl proton)], and <sup>13</sup>C n.m.r. in C<sub>6</sub>D<sub>6</sub>-Et<sub>3</sub>N, 19:1 [distinctive features were resonances at 159.8 (C-1), 155.8 (C-6), 137.2 and 130.6 (C-13,14), 95.3 (C-5), 84.1 (C-15) 77.3 and 72.2 (C-9,11) and 51.1 (Me ester)p.p.m. from TMS], and since it is produced by a *trans*-elimination<sup>13</sup> of HI from (4), it must therefore be the (5Z) compound (5b).

Reaction of (4) with sodium methoxide<sup>14</sup> also yielded the ester (2b), together with some of the Na salt (2c), and was the basis of what proved to be a simple procedure for the production of the pure Na salt (2c) in high yield. Thus, the iodo-ester (4) (500 mg.) was stirred with

methanolic NaOMe [prepared from Na (0.23 g., 10 equivs.) and MeOH (3.5 ml.)] under  $N_2$  at room temperature overnight; 1N aq. NaOH (2.5 ml.) was added to the yellow reaction solution to bring about hydrolysis of the ester moiety and, after 2 hours, the methanol was evaporated in vacuo at room temperature. The residual aqueous solution gave rise spontaneously to a mass of colourless fine needles of the Na salt (2c) which was cooled ( $0^\circ$ ), collected, washed sparingly with 1N aq. NaOH<sup>15</sup>, air-dried, and stored in a stoppered tube; this salt (383 mg.) had  $\nu_{\max}$  (KBr disc)  $1692\text{ cm}^{-1}$  ( $O=C-C\backslash$ ) and twenty  $^{13}\text{C}$  resonances only were observed [at 182.7 (C-1), 158.2 (C-6), 140.0 and 134.3 (C-13,14), 100.7 (C-5), 87.5 (C-15), 80.6 and 75.5 (C-9,11), 58.0 (C-12), 49.0, 45.8, 42.4, 41.9, 37.5, 35.8 (C-18), 31.6, 29.9, 29.3, 26.7 (C-19), and 18.4 (C-20) p.p.m. from TMS in  $\text{DMSO-d}_6$ ]. The product (2c) thus obtained completely inhibited arachidonic acid-induced platelet aggregation (human platelet-rich plasma) at 1 ng./ml. and its profile of biological activity on the rabbit aorta, rabbit coeliac artery, rat stomach strip and rat colon was as expected from the results previously obtained<sup>4</sup>.

Exposure of the Na salt (2c) to dilute aqueous mineral acid yielded colourless crystals, m.p. 101-105.5<sup>o</sup>, of 6-oxo-PGF<sub>1 $\alpha$</sub> <sup>4,5,16</sup> (5a) [Found: C, 64.68; H, 9.39.  $\text{C}_{20}\text{H}_{34}\text{O}_6$  requires C, 64.84; H, 9.25%]. In  $\text{DMSO-d}_6$ , the  $^{13}\text{C}$  resonances point to its existence as a mixture of 4 tautomers: the keto-form (ca 40%) and three lactol forms<sup>17</sup> (40%, 10%, 10%). The electron-impact mass spectrum of its methoxime, as the tris-Me<sub>3</sub>Si derivative, was identical with that recorded in the literature<sup>18</sup>.

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7. Prepared by esterification of PGF<sub>2 $\alpha$</sub>  (Cambrian Chemicals) with diazomethane.
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9. In contrast, the carboxylic acid of the corresponding bromo-compound, obtained by interaction of  $\text{PGF}_{2\alpha}$  with N-bromosuccinimide, was identified (t.l.c.,  $^1\text{H}$  n.m.r.) as a mixture of 2 compounds.
  10. The vinyl ether is transformed by this acidic medium into the polar 6-oxo- $\text{PGF}_{1\alpha}$  methyl ester ( $5b$ ),  $r_f 0.135$  relative to  $r_f 0.32$  for the starting material.
  11. Merck Kieselgel 60.
  12. Resolution enhancement (A.J. Everett and A.G. Ferrige, unpublished technique) was necessary for the extraction of coupling constants.
  13. The same elimination product ( $2b$ ) would be produced whether the iodo-ester has the configuration ( $4a$ ) or ( $4b$ ).
  14. KOH/EtOH has been used for dehydrohalogenation of 2-halo-ethers (A.R. Katritzky, M.J. Sewell, R.D. Topsom, A.M. Monro, and G.W.H. Potter, *Tetrahedron*, 1966, 22, 931).
  15. The Na salt is very soluble in  $\text{H}_2\text{O}$ . After air-drying, the product has a surface coating of  $\text{Na}_2\text{CO}_3$  (ca 3.5% by weight) which protects the vinyl ether moiety against  $\text{CO}_2$ -catalysed hydrolysis.
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  17. The structural formula depicts the two possible furanose lactols. The existence of a third, pyranose, lactol involving the 6-oxo- and 11-hydroxy groups should be considered.
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- \* Publication delayed at the author's request.