

## A 16-*p*-fluorophenoxy prostanoid with potent and long-lasting thromboxane-like actions

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Replacement of the C17–C20 unit in both prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) and PGD<sub>2</sub> with a *p*-fluorophenoxy group increases thromboxane-like activity by 50–100-fold (Jones & Marr, 1977). This surprising result prompted us to determine the effect of a similar substitution on the potencies of compounds with ring structures closer to the cyclic endoperoxides/thromboxanes. We therefore prepared the 9,11-etheno-16-*p*-fluorophenoxy analogue of PGH<sub>2</sub> (based on the synthetic route of Leeney, Marsham, Ritchie & Senior, 1976), in view of the weak thromboxane-like activity reported for 9,11-etheno PGH<sub>2</sub> itself (Corey, Shibazaki, Nicolaou, Malmsten & Samuelsson, 1976).

Like 11,9-(epoxymethano) PGH<sub>2</sub> (Upjohn 46619) (Bundy, 1975) and 9,11-etheno PGH<sub>2</sub> (ICI 86841) our novel compound contracted the rabbit aortic strip. However, comparisons of potency were difficult to make because of slow reversal of the contractile action of the 9,11-etheno-16-*p*-fluorophenoxy analogue. This is shown in Figure 1. Similar results were obtained for the contractile action on guinea-pig tracheal chain.

On citrated human platelets the 9,11-etheno-16-*p*-fluorophenoxy analogue caused rapid and reversible aggregation at concentrations of 50–100 ng/ml and irreversible aggregation at higher concentrations (Born aggregometer). It was equipotent with 11,9-(epoxymethano) PGH<sub>2</sub> and 15 times more active than 9,11-etheno PGH<sub>2</sub>. No differences in the time courses of the responses were seen; this is not unexpected

considering the dynamic nature of the platelet system (either reversible or irreversible aggregation occurs and an equilibrium state of partial aggregation cannot be produced).

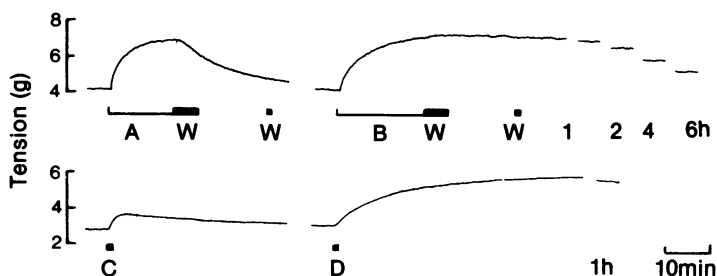
The 9,11-etheno-16-*p*-fluorophenoxy analogue was toxic to rats (abdominal writhing, ataxia, respiratory distress, cyanosis) at doses of 10–50 µg/kg i.p., and caused death within 15 to 60 min at doses of 100–500 µg/kg i.p.

The nature of the long-lasting contractile activity of the 9,11-etheno-16-*p*-fluorophenoxy analogue is under investigation. It is obvious that care is required in the handling of such noxious substances in the laboratory, and that newly synthesized prostanoids should be screened for thromboxane-like activity as soon as is possible.

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### References

- BUNDY, G.L. (1975). Synthesis of prostaglandin endoperoxide analogs. *Tetrahedron Lett.*, 1957–1960.
- COREY, E.J., SHIBAZAKI, M., NICOLAOU, K.C., MALMSTEN, C. & SAMUELSSON, B. (1976). Simple, stereocontrolled total synthesis of a biologically active analog of the prostaglandin endoperoxides (PGH<sub>2</sub>, PGG<sub>2</sub>). *Tetrahedron Lett.*, 737–740.
- JONES, R.L. & MARR, C.G. (1977). Actions of 16-aryloxy analogues of prostaglandin F<sub>2α</sub> on preparations responsive to prostaglandin endoperoxides. *Br. J. Pharmac.*, 61, 694–696.
- LEENEY, T.J., MARSHAM, P.R., RITCHIE, G.A.F. & SENIOR, M.W. (1976). Inhibitors of prostaglandin biosynthesis. A bicyclo-[2.2.1]-heptene analogue of '2' series prostaglandins and related derivatives. *Prostaglandins*, 11, 953–960.



**Figure 1** Rabbit aortic strips suspended in Krebs–Henseleit solution at 37°C and aerated with 95% O<sub>2</sub>/5% CO<sub>2</sub>. Isometric recording. Upper trace: organ bath (5 ml) with wash (W) by overflow. A, 11,9-(epoxymethano) PGH<sub>2</sub>, 15 ng/ml. B, 9,11-etheno-16-*p*-fluorophenoxy PGH<sub>2</sub>, 15 ng/ml, preparation washed every 15 minutes. Lower trace: superfusion at 10 ml/minutes. C, 11,9-(epoxymethano) PGH<sub>2</sub>, 20 ng over 15 seconds. D, 9,11-etheno-16-*p*-fluorophenoxy PGH<sub>2</sub>, 20 ng over 15 seconds. The 9,11-etheno-16-*p*-fluorophenoxy PGH<sub>2</sub> responses are 70–80% of the maximal response.