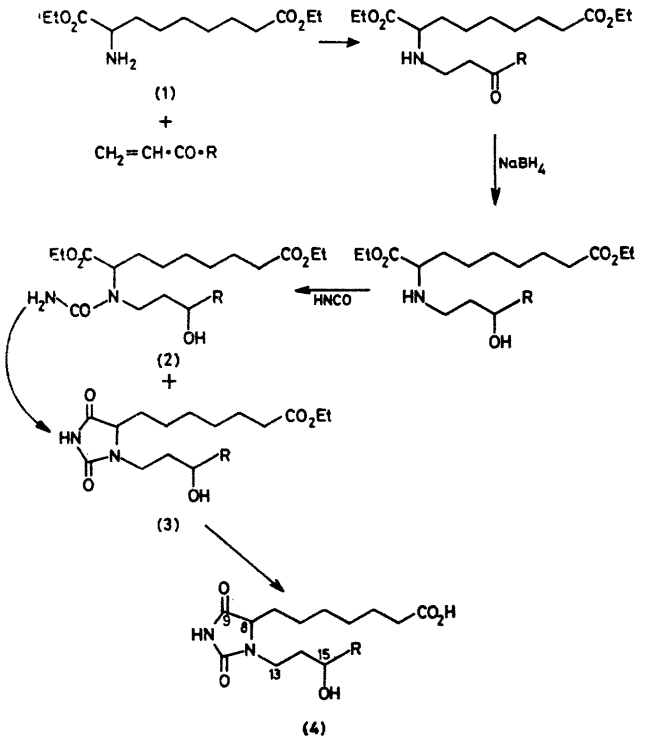
Hydantoin Prostaglandin Analogues, Potent and Selective Inhibitors of Platelet Aggregation

By A. GORDON CALDWELL, C. JOHN HARRIS, RAY STEPNEY, and NORMAN WHITTAKER*
(*Wellcome Research Laboratories, Beckenham, Kent* BR3 3BS)

Summary A series of biologically very active hydantoin prostaglandin analogues has been synthesised for which the relationship between potency and absolute stereochemistry has been elucidated.

MUCH effort has been directed towards the development of therapeutically useful prostaglandin analogues having only one of the varied and powerful biological actions of the natural compounds, but with limited success. In this communication we describe the synthesis of some hydantoin prostaglandin analogues which are very potent inhibitors of platelet aggregation and, in addition, have appreciable selectivity of action.

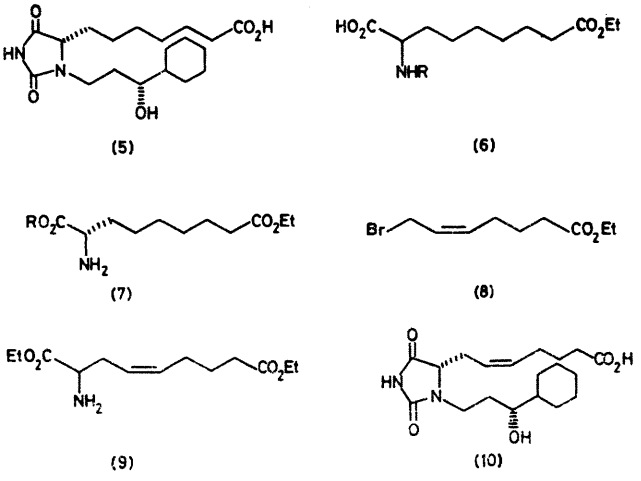


SCHEME. R = Alkyl, branched alkyl, or cycloalkyl.

The amino-diester (**1**)[1] has been shown to react smoothly with vinyl ketones at room temperature and in each case the resulting Mannich base was converted (Scheme) in 2 steps in good overall yield into a mixture of hydantoic ester (**2**) with hydantoin (**3**). Heating of the mixture at 100 °C completed the conversion into hydantoin and hydrolysis of the residual ester function with aqueous alkali at room temperature then gave the carboxylic acid (**4**) as a mixture of two racemic diastereoisomers, distinguishable by t.l.c. and separable by h.p.l.c. The diastereoisomers also showed characteristic differences in their ^{1}H n.m.r. spectra, the C-13 protons† in the less polar species exhibiting a greater degree of non-equivalence. The diastereoisomers are crystalline solids, stable in acid solution and interconvertible, through epimerisation at C-8, by base.

For each variant of R in (**4**), the less polar diastereoisomer had the greater biological potency. The less polar diastereoisomer of (**4**, R = pentyl), for example, had twice the potency of prostaglandin E_1 (PGE_1) as an inhibitor of platelet aggregation in human platelet-rich plasma and the corresponding cyclohexyl analogue (**4**, R = cyclohexyl) was *ca.* 14 times as potent as PGE_1. These compounds also have selectivity of action, causing less vasodilatation than PGE_1 in experimental animals.

X-Ray crystal structure analysis of the less polar, *i.e.* more potent diastereoisomer of (**4**, R = cyclohexyl) has established that its relative stereochemistry at C-8 and C-15 is that depicted in formula (**5**). Further, it has been demonstrated by total synthesis that the biological activity resides in the (+)-enantiomer with the absolute configuration shown in (**5**), corresponding to that in PGE_1.



Treatment of the racemic amino-diester (**1**) with water containing <1 equiv. of acetic acid at 100 °C for a few hours gave the amino-acid (**6**, R = H) smoothly and exclusively. Exposure of its *N*-acetyl derivative (**6**, R = Ac) to the action of porcine renal acylase I liberated the (*S*)-amino-acid (**7**, R = H), $[\alpha]_D^{25}$ + 23·5° (*c* 1 in HOAc) in 86% yield and esterification with ethanol–thionyl chloride gave the required (*S*)-amino-diester (**7**, R = Et), $[\alpha]_D^{21}$ + 16·3° (*c* 1 in EtOH). Application of the reaction sequence (Scheme) to (**7**, R = Et), with separation of the epimeric amino-alcohols formed in the borohydride reduction, then yielded the hydantoin (**5**), $[\alpha]_D^{23}$ + 22·6° (*c* 1 in EtOH).

† Prostanoic acid numbering.

On the basis of the observed correlation of chromatographic polarity with n.m.r. characteristics and biological activity, it is inferred that the same relationship of stereochemistry to biological activity applies throughout the series.

The racemic (5*Z*)-5,6-didehydro analogue of (**4**, R = cyclohexyl) was obtained from the bromo-ester (**8**)[2] *via* the amino-diester (**9**). Its less polar diastereoisomer, formulated as (±)-(**10**), had remarkable activity; it had *ca.* 22 times the anti-aggregatory potency of PGE_1, caused less vasodilatation than PGE_1 and, moreover, was virtually inactive on intestinal smooth muscle.

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