COMUNICACION ORIGINAL

(±)-9-Deoxy-10,12-diaza-13,14-dihydro-16-cyclohexyl-ω-pentano prostaglandin D_1 and the 2,3-Dehydro Derivative Thereof. New Powerful Inhibitors of ADP Induced Platelet Aggregation[1].

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RESUMEN

Se sintetizaron la (+) -9-desoxi-10,12-diaza-13,14-dihidro16-ciclohexil -ω-pentanorprostaglandina D1 (3a) y el correspondiente análogo Δ^2 (13c) a partir del 8-azido-9 hidroxinonanoato de metilo (4a). Estos compuestos resultaron ser respectivamente 2.2 y 2.6 veces más activos que la PGE_1 como inhibidores *in vitro* de la agregación de plaquetas inducida por ADP en plasma humano, pero fueron inactivas cuando se administraron a conejillos de indias por vía oral, a dosis hasta de 2 mg/kg.

ABSTRACTS

(+) -9-Deoxy-10,12-diaza-13,14-dihydro-16-cyclohexyl-ω-pentanorprostaglandin D_1 (3a) and the trans-Δ^2-analog 13c thereof were synthesised from methyl 8-azido-9-hydroxinonanoate (4a). These compounds were 2.2 and 2.6 -fold more active, respectively, than PGE_1 as inhibitors of ADP induced aggregation of human platelet rich plasma *in vitro*, but were inactive in guinea pigs on oral administration at doses up to 2 mg/kg.

INTRODUCTION

The hydantoin prostanoid 1 (BW245C) is a potent inhibitor of adenosine diphosphate (ADP) induced blood platelet aggregation *in vitro* and *in vivo*[2], and action which is probably mediated by PGD_2 receptors[2 3]. Intravenous (i.v.) administration of this compound to man, elicited vasodilatation and platelet aggregation inhibition which were qualitatively similar to those of PGI_2 but the duration of these effects was longer[4]. Repeated oral dosing (150 μg. q.i.d. for 5 days) provoked side effects such as headache, facial flushing, nasal congestion, abdominal discomfort and tachycardia but had no significant effect on platelet aggregation inhibition[5].

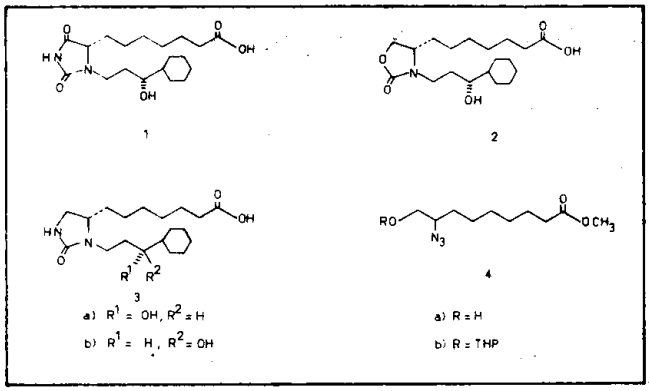
This side effect profile makes it unlikely that BW245C will be used as an oral alternative to i.v. PGI_2.

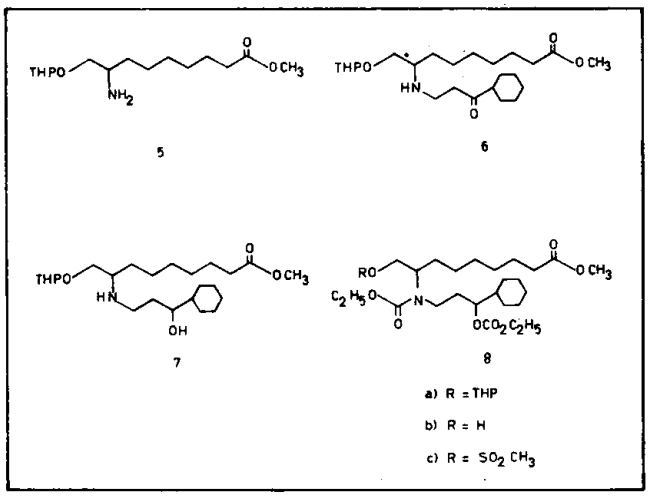
It is known that PGD_2 and the 9-deoxy analog thereof are equipotent as hypotensive agents and as inhibitors of ADP induced platelet aggregation (*in vitro*)[6]. In addition, it was recently reported that 2, the 9-deoxy-10-oxa analog of BW245C, was a highly active inhibitor of ADP induced platelet aggregation [human platelet rich plasma (HPRP)/ *in vitro*[7]. It was thus obvious that the synthesis and biological evaluation of 3a, the 9-deoxy congener of 1 would be of considerable interest[8].

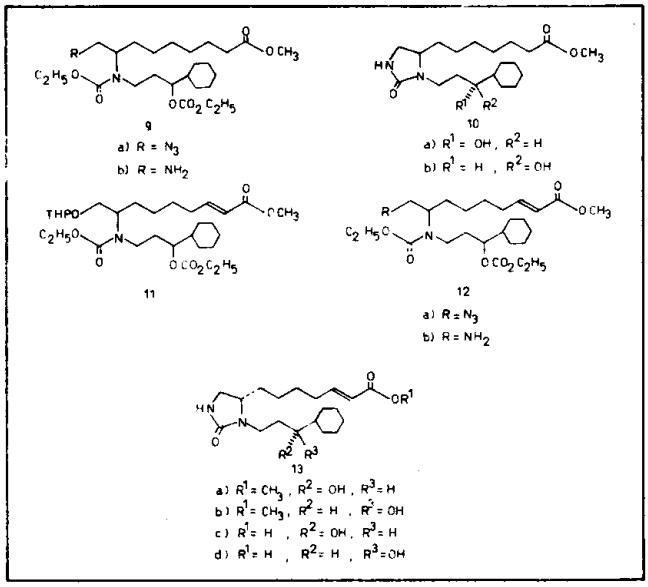
DISCUSSION & RESULTS

The starting point for the synthesis of 3a was the known[7] azido alcohol 4a, which was converted into the tetrahydropyranyl ether 4b at 0°C (1h., TsOH) in dichloromethane solution[9]. Catalytic reduction of this compound (10% Pd-C, 40 p.s.i.g.) in metanol solution gave the amine 5, which was added conjugatively to cyclohexyl vinyl ketone[10]. (1.1 equiv.) at room temperature, in THF solution containing tetramethylguanidine (25 mol. %). The solution of the unstable aminoketone 6 thus generated was added to cold methanolic sodium borohydride to give the monoprotected amino diol 7 in 62% yield from 5. This material was reacted with excess ethyl chloroformate (pyridine, 0°C) and the diacylated product 8a [IR ($CHCl_3$) 1735,1685 cm^{-1}] was subjected to acidic hidrolysis [HOAc, THF, H_2O (3:1:1)] to remove the tetrahydropyranyl group. The primary alcohol 8b (31% from 7, inseparable mixture of diastereoisomers [IR ($CHCl_3$) 3540, 1740, 1685 cm^{-1}] was converted into the methanesulfonate 8c with excess (2.6 equiv.) methanesulfonyl chloride (CH_2Cl_2, Et_3N, 0 °C) and thence, without purification, into the azide 9a [73%, IR ($CHCl_3$) 2065, 1738, 1690 cm^{-1}; NMR ($CDCl_3$) δ 3.00-3.4 (m, 4H; CH_2N_3,CH_2NJ, 3.83 (m, 1H, CHN), 4.53 (m, 1H, $CHOCO_2Et$)] with NaN_3 in boiling acetonitrile. Catalytic reduction of 9a, as described above, gave the amine 9b (67%) which was cyclized with aqueous methanolic sodium hydroxide (4 equiv.) at reflux temperature (18 h). The crude product was esterified with ethereal diazomethane and the diastereoisomeric esters were sepa-

rated by preparative thin layer chromatography (TLC) on silica gel (EtOAc). The less and more polar esters 10a [IR ($CHCl_3$) 3420, 1735, 1685 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (m, 2H, CH_2NH), 3.50 (m, 2H, CH_2N), 4.08 (m, 1H, CHOH)] and 10b (spectroscopic properties very similar to 10a) were obtained in 33 and 38°/o yields, respectively.







Saponification of the esters was effected at room temperature with aqueous methanolic sodium hydroxide (2 equiv.) to give the carboxylic acids 3a and 3b in ca 85°/o yield.

The synthesis of the Δ^2-analog of 3a was also undertaken because unsaturation of this site might be expected to slow down the metabolic degradation of the α-chain. The trans double bond was introduced into the upper side chain at an early stage in the synthesis using a procedure modeled after that described by Grieco, et al.[11]. Thus, the fully protected, open chain ester 8a was reacted sequentially with 2 equiv. of lithium diisopropylamide in THF solution (-78 °C), diphenyl diselenide (2 equiv, 20 min., -78 °C) and excess 30°/o hydrogen peroxide [EtOAc-MeOH (3:2), 45 °C, 20 min.] to give the unsaturated ester 11 in 76°/o overall yield. This material was then converted into the mixture of diastereoisomeric azido compounds 12a by a sequence of reactions identical to that used for the synthesis of 9a. The azide was reduced with zinc dust in methanol at room temperature and the amine 12b (43°/o yield) was converted into the oxazolidinones 13a [IR ($CHCl_3$) 3450, 1735, 1685 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (m, 2H, CH_2NH), 3.58 (m, 2H. CH_2N), 5.85 (d, 1H, J=15 Hz, H-2)] and 13b (more polar) in 32 and 24°/o yields, respectively, which were separable by TLC as described above for the saturated analogs. The carboxylic acids 13c and 13d were obtained by saponification of the esters in the usual way.

The less polar esteres of the imidazolidinones 10a and 10b and 13 a and 13 b were assigned the α-stereochemistry at C-15 because the biologically more active carboxylic acids were obtained therefrom on saponification. All of the acids inhibitec the ADP induced aggregation of HPRP *in vitro* (Table 1) in a dose dependent manner[12] and the 15α-isomers 3a and 13c were about 2-and 3-fold more potent than PGE_1 in this regard. Oral administration of either of these compounds to male anesthetized guinea pigs, at doses up to 2 mg/kg, did not, however, show significant inhibition of ADP induced platelet aggregation (*ex vivo*)[13].

Table 1. Innibition of ADP Induced Aggregation of Human Blood Platelet Rich Plasma by (±) 9-Deoxy-10,12-diaza-13, 14-dihydroprostaglandin D_1 Derivatives.

compound no.	TLC mobility of methyl esters[a]	relative potencyb
PGE_1		1[c]
3a	-p (10a)	2.2
3b	+p (10b)	0.2
13c	-p (13a)	2.6
13d	+p (13b)	0.1

[a]Silica gel as stationary phase, ethyl acetate as solvent.

[b]Relative activity of the prostanoic acid derivative derived from the methyl ester of the indicated TLC mobility.

[c]IC_{50} for PGE_1 = 8.5 X 10^{-8} M.

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