Imidazolidin-2-one Prostaglandin Analogues

Paul Barraclough, William P. Jackson, and (in part) C. John Harris

Department of Medicinal Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS

Received May 18, 1990

The 5-desoxy analogue of BW245C, imidazolidin-2-one **3**, has been synthesized by reduction of the *N*-benzyl hydantoin derivative **6**. Compound **3** was found to be approximately equipotent with BW245C as an inhibitor of platelet aggregation and this result indicates that the 5-keto group of BW245C is not essential for platelet inhibitory activity.

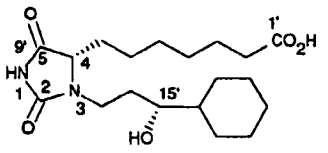
Imidazolidin-2-on als Prostaglandin Analogon

Das 5-Desoxyanalog von BW245C, das Imidazolidin-2-on **3**, ist durch Reduktion des *N*-Benzylhydantoinderivates **6** synthetisiert worden. Verbindung **3** hat annähernd die gleiche Wirksamkeit als Plättchenaggregationshemmer wie BW245C. Dieses Ergebnis zeigt, daß die 5-Ketogruppe in BW245C für die Plättchenhemmung nicht erforderlich ist.

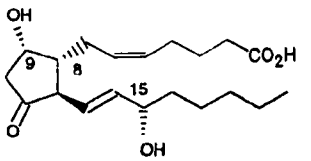
The hydantoin prostaglandin (PG) analogue BW245C **1** is a potent inhibitor of human platelet aggregation[1]. BW245C is also a PGD_2 (2)-agonist[2] and has undergone preliminary clinical evaluation in human volunteers[3]. These findings stimulated a detailed investigation into the structure-platelet anti-aggregating activity relationships of the hydantoin PG series. Previous studies have investigated the effects of replacing the hydantoin ring by other, similar, heterocycles[4] and the effects of modifying the carboxy group[2] of BW245C. We now report the results of an investigation intended to find out whether the 5*(9')+keto group of BW245C is required for platelet anti-aggregating properties. This study thus necessitated the synthesis of the analogue **3**.

Chemistry

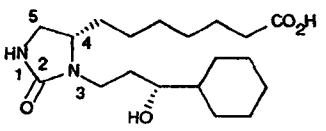
The synthesis of the 5-desoxy analogue **3** was achieved as shown in Scheme 1. Numerous attempts to reduce BW245C **1** directly to acid **10** with $LiAlH_4$ or $NaBH_4$ were unsuccessful. Protection at N-1 therefore seemed necessary to prevent anion formation and facilitate reduction of the hydantoin to the imidazolinone. Even reduction of hydantoin **6** to **7** with $NaBH_4$ required the presence of acetic acid to generate the more reactive sodium acetoxyborohydride[5]. This observation is in contrast to that for the *N*-1-methyl derivative[1] of BW245C where reduction proceeds smoothly to the corresponding imidazolinone with $NaBH_4$ alone. In addition small amounts (3%) of the alcohol by-product **8** were obtained on reduction of **6**. Removal of the benzyl protecting group of **9** using sodium in ammonia gave imidazolinone **10**. Reduction of the double bond of **10** was accomplished in 90% yield using triethylsilane-trifluoroacetic acid[6] to give a mixture of the diastereomers **3** and **11**. The individual diastereomers could not be separated from this mixture by HPLC and so the above reaction sequence was modified as shown in Scheme 2. Reduction of the double bond of ester **7** led to a mixture of the *N*-benzyl imidazolidinones **12** and **13**. The individual diastereomers were readily separable from this mixture by flash chromatography. Subsequent saponification of **12** and **13** followed by debenzylation gave the two pure diastereomers **3** and **11**. The less polar ester **12** was converted to an acid **3** which displayed far more potent PG mimetic pharmacological properties than the acid



(1) BW245C



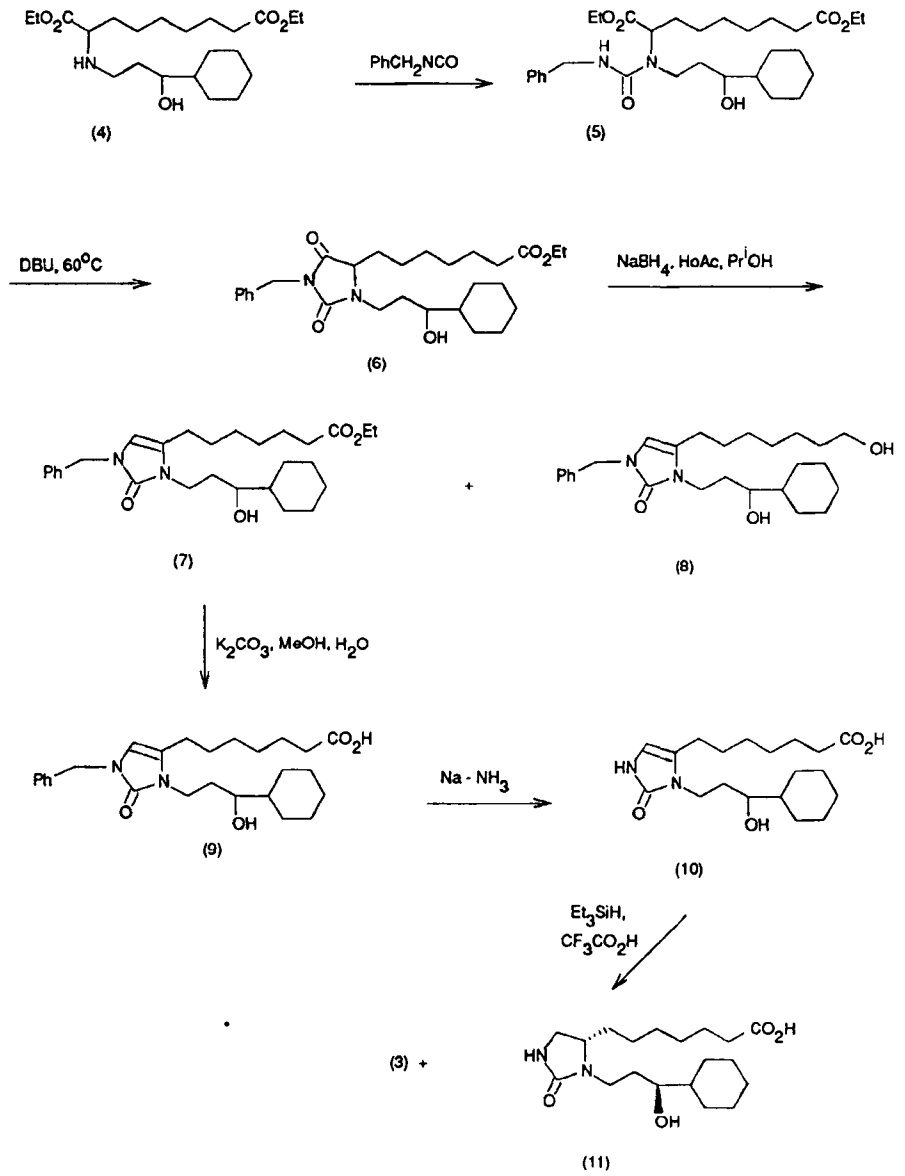
(2)



(3)

* IUPAC numbering;
\+ PG numbering; all compounds are racemic.

  0365-6233/91/0808-0473 $ 3.50 + .25/0



Scheme 1

derived from the more polar epimer **13**. Compounds **3** and **12** were thus assigned the same relative stereochemistry (at C-4 and C-15') as for BW245C (4S,15'R) and PGD_2 (at C-8 and C-15). Since the completion of this work an alternative synthesis of **3** has been reported[7].

Structure - activity relationships

The ability of the diazaprostaglandin analogues **1**, **3**, **10**, and **11** to inhibit ADP-induced platelet aggregation was measured *in vitro* with human platelet rich plasma. These analogues were also tested for their blood pressure lowering effects in normotensive anaesthetized rats. Results are given in the Table.

Imidazolinone **10** proved to be a weak inhibitor of platelet aggregation. This observation is consistent with previous findings[4] which show that replacement of the chiral C-4 carbon centre by a N-atom leads to a drastic reduction in activity.

In contrast the desoxy analogue **3** was found to be slightly less active than BW245C as an inhibitor of human platelet aggregation. This result demonstrates that the O-atom of the 5-carbonyl group of BW245C is not a critical structural moiety for platelet antiaggregating activity. Interestingly, Bundy[8] has shown that the 9 α-hydroxy group of PGD_2 is not required for anti-aggregatory activity, 9-deoxy-PGD_2 being more potent than PGD_2. Analogue **3** also displayed vasodilatory properties but was only approximately 0.1 times as potent as BW245C in its ability to lower blood pressure in the anaesthetized rat. If this reduced hypotensive effect is also expressed in man compound **3** will be a more selective inhibitor of human platelet aggregation than BW245C. The conclusion from this study is that the 5-carbonyl group of BW245C is not necessary for platelet effects but this moiety is required for hypotensive activity *in vivo*.

We are grateful to Dr. *B. R. J. Whittle* for the pharmacological data, Mr. *P. R. W. Baker* for the microanalytical data, and Mr. *C. J. Wharton* for valuable discussions.

Experimental Part

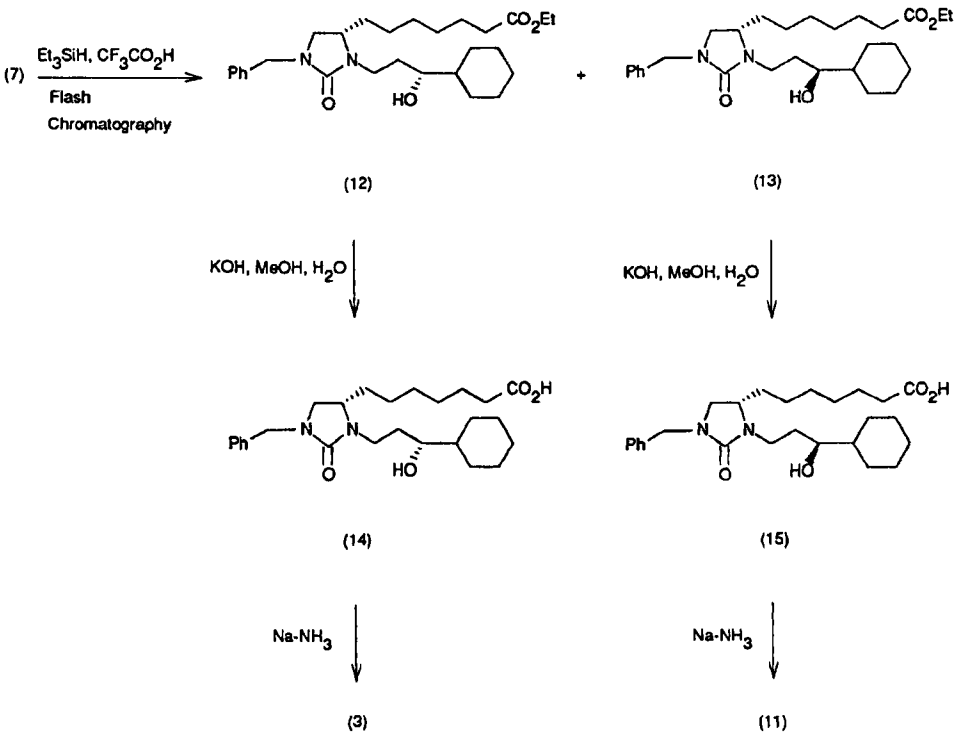
Melting points: Koffler hot-stage instrument, uncorrected.- ^{1}H-NMR spectra: Bruker HFX 90 (90 MHz), Bruker AM-200 (200 MHz) or WM-360 (360 MHz) instruments, TMS as internal standard.- E.I. mass spectra: Kratos MS-25 instrument at 70 eV. FAB mass spectra: as described[2]. Thin layer chromatograms (t.l.c.): Merck silica gel $60F_{254}$, developed with iodine or phosphomolybdic acid. Flash chromatography: silica gel (230-400 mesh).

Ethyl 1-Benzyl-3-(3-cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidineheptanoate (6)

To diethyl 2-(3-cyclohexyl-3-hydroxypropyl)aminononanedioate[1] (4) (19.0 g, 0.048 mol) in dry toluene (30 ml) was added dropwise, over 0.5 h, a solution of benzyl isocyanate (6.97 g, 0.052 mol) in toluene (30 ml) with external cooling (ice bath). The resulting solution was then stirred at room temp. until t.l.c. indicated that formation of urea **5** was complete (ca. 2 h). 1,8-Diazabicyclo[5.4.0]undec-7-ene (7.25 g, 0.048 mol) was then added, the reaction mixture stirred at room temp. for 16 h and then at 60°C for 1 h under N_2. After dilution with ethyl acetate (250 ml) the org. layer was washed with 2 N HCl (100 ml) and then saturated NaCl solution. The extract was then dried over $MgSO_4$, the solvent removed *in vacuo* and the residue flash chromatographed on silica, eluting with ether-hexane (7:3) to give 6.7 g (29%) of the less polar diastereomer of **6** as a pale yellow syrup, R_f 0.60 (silica, ether).- $C_{28}H_{42}N_2O_5$ (486.6).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 0.80-2.05 (23H, m, aliphatic H), 1.24 (3H, t, J = 7 Hz, Me), 2.25 (2H, t, J = 7 Hz, CH_2CO), 2.73 (1H, br.d, J = 5 Hz, OH, exchangeable), 2.89-3.34 (2H, m, NCHH + CHOH), 3.72-4.05 (2H, m, NCHH + CHN), 4.11 (2H, q, J = 7 Hz, OCH_2), 4.64 (2H, AB m, CH_2Ph), 7.18-7.45 (5H, m, Ph).- MS: m/z = 486 (M^+).- Further elution gave 6.1 g (26%) of the more polar diastereomer of **6** as a pale yellow syrup, R_f 0.55 (silica, ether).- $C_{28}H_{42}N_2O_5$ (486.6).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 0.80-2.05 (23H, m, aliphatic H), 1.24 (3H, t, J = 7 Hz, Me), 2.25 (2H, t, J = 7 Hz, CH_2CO), 2.68 (1H, v.br.peak, OH, exchangeable), 3.20-3.59 (3H, m, NCH_2 + CHOH), 3.98 (1H, t, J = 4 Hz, CHN), 4.11 (2H, q, J = 7 Hz, OCH_2), 4.61 (2H, s, CH_2Ph), 7.18-7.45 (5H, m, Ph).

Ethyl 1-Benzyl-3-(3-cyclohexyl-3-hydroxypropyl)-2-oxo-4-imidazolineheptanoate (7) *and 1-benzyl-3-(3-cyclohexyl-3-hydroxypropyl)-2-oxo-4-imidazolineheptanol* (8)

To a solution of the hydantoin **6** (15.0 g, 0.03 mol) in isopropanol (150 ml) was added $NaBH_4$ (5.05 g, 0.13 mol) in portions over 15 min while stirring. The resulting mixture was then treated dropwise with a solution of acetic acid (10 ml) in isopropanol (50 ml) over 0.5 h and stirring was then continued for a further 3 h. More $NaBH_4$ (2.0 g) was then added followed by acetic acid (5 ml) dropwise during 30 min and the mixture was then stirred at room temp. overnight. 2 N HCl (200 ml) and ethyl acetate (200 ml) were stirred together and the above reaction mixture added. The org. layer was separated, the aqueous phase extracted with ethyl acetate, and the combined org. extracts washed with sat. NaCl solution. After drying over $MgSO_4$, the extract was evaporated and the residual oil flash chromatographed on silica. Elution with ether-hexane (4:1) gave 8.1 g (56%) of **7** as a pale yellow oil, R_f 0.4 (Et_2O).- $C_{28}H_{42}N_2O_4$ (470.6).- $\tilde{\nu}$max (film) 3360 (br) (OH), 1732, 1668 (carbonyls), 1626 (olefin) cm^{-1}.- ^{1}H-NMR (90 MHz, $CDCl_3$, 50°C): δ (ppm) = 0.80-2.05 (21H, m, aliphatic H), 1.25 (3H, t, J = 7 Hz, CH_3), 2.27 (4H, br.t, J = 7 Hz, CH_2CO + CH_2C=C), 3.18 (1H, m, CHOH), 3.41-3.75 (1H, NCHH), 3.82-4.36 (3H, m, OCH_2 + NCHH), 4.75 (2H, s, CH_2Ph), 5.82 (1H, br.s, NCH=C), 7.10-7.48 (5H, m, Ph).- MS: m/z = 470 (M^+). Further elution using ether-ethyl acetate (1:1) gave 0.45 g (3%) of **8** as a pale yellow oil, R_f 0.2 (Et_2O).- $C_{26}H_{40}N_2O_3$ (428.6).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 0.75-2.10 (25H, m, aliphatic H + 2x OH, 2H exchangeable), 2.30 (2H, t, J = 7 Hz, CH_2C=C), 3.14 (1H, m, CHOH), 3.34-3.55 (1H, m, NCHH), 3.61 (2H, t, J = 7 Hz, CH_2OH), 3.86-4.30 (1H, m, NCHH), 4.75 (2H, s, CH_2Ph), 5.80 (1H, br.s, NCH=C), 7.09-7.45 (5H, m, Ph).- MS: m/z = 428 (M^+).



Scheme 2

1-Benzyl-3-(3-cyclohexyl-3-hydroxypropyl)-2-oxo-4-imidazolineheptanoic acid (9).

Ester 7 (2.63 g, 5.6 mmol), methanol (20 ml), water (10 ml) and K_2CO_3 (3.0 g, 22 mmol), were heated at reflux for 1 h. The solvent was removed *in vacuo*, the residue diluted with water and washed twice with ether. 2 N HCl was added to the aqueous solution and the oil extracted twice with ethyl acetate. The combined org. extracts were washed with sat. NaCl solution, dried over $MgSO_4$ and evaporated to yield 2.1 g of crude 9.

3-(3-Cyclohexyl-3-hydroxypropyl)-2-oxo-1H-4-imidazolineheptanoic acid (10)

Sodium wire (0.3 g, 13 mmol) was added to liquid ammonia (50 ml) and stirred at reflux for 20 min. A solution of acid 9 (2.10 g, 4.8 mmol) in dry tetrahydrofuran (15 ml) was then added dropwise to this suspension at such a rate that a permanent blue colour persisted. The mixture was stirred at reflux for 1 h, isopropanol (2 ml) added, and the mixture allowed to warm to room temp. Water was then added to the residual mixture followed by conc. HCl until the whole was at pH 1. The mixture was then extracted twice with chloroform, the combined extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Recrystallisation of the residual solid from ethyl acetate-hexane gave 1.0 g (60%) of 10, m.p. 115-116°C.- $C_{19}H_{32}N_2O_4$ (352.5) Calc. C 64.7 H 9.15 N 7.8 Found C 64.9 H 9.17 N 7.9%.- ^{1}H-NMR [90 MHz, $(CD_3)_2SO$]: δ (ppm) = 0.75-1.90 (21H, m, aliphatic H), 2.10-2.40 (4H, m, CH_2CO + CH_2C=C), 3.09 (1H, m, CHOH), 3.55 (2H, t, J = 7 Hz, NCH_2), 6.02 (1H, br.s, NCH=C), 9.70 (1H, br.s, NH, exchangeable).

(±)-(S,R*) and (±)-(S*,S*)3-(3-Cyclohexyl-3-hydroxypropyl)-2-oxo-4-imidazolidineheptanoic acid* (3) *and* (11)

Acid 10 (0.35 g, 1.0 mmol), trifluoroacetic acid (1.5 ml) and triethylsilane (0.2 ml, 1.3 mmol), were heated at 50°C for 8 h. More triethylsilane (0.2 ml) was then added and heating continued at 50°C for further 3 h. After cooling to room temp. the excess reagents were removed *in vacuo* and the residue stirred with acetic acid (6 ml) and water (2 ml) at room temp. for 3 h. Volatile material was then removed *in vacuo* to yield an oil which was shown by t.l.c. to be a mixture, and which appeared from its i.r. and n.m.r. spectra to contain the trifluoroacetyl derivatives of acids 3 and 11 as major components. This oil was stirred with methanol (2 ml), water (2 ml) and K_2CO_3 (1 g) at room temp. overnight. The methanol was removed *in vacuo*, the residue acidified with 0.1 N HCl and then extracted twice with ethyl acetate. After washing with sat. NaCl solution the combined extracts were dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography of the residual oil on silica, eluting with $CHCl_3$-MeOH (9:1) gave 0.31 g (89%) of 3, 11 as an oil. T.l.c. examination of this material, in a variety of solvent systems, showed little if any separation of the diastereomers.

Ethyl1-Benzyl-3-(3-cyclohexyl-3-hydroxypropyl)-2-oxo-4-imidazolidine-heptanoate (12), (13)

Ester 7 (4.0 g, 8.5 mmol) was reduced with triethylsilane (2 ml) - trifluoroacetic acid (15 ml) by a procedure similar to that used for preparing acids 3 and 11. The crude product was a yellow oil (3.4 g) which was separated into the component diastereomers by flash chromatography on silica, eluting with ether-hexane (3:1) to give firstly the less polar diastereomer 12 (R_f 0.33) as an oil (0.9 g, 22%).- $C_{28}H_{44}N_2O_4$ (472.6).- $\tilde{\nu}$ max (film) 3420 (br) (OH), 1735 (ester C=O), 1678 (carbonyl) cm^{-1}.- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 0.90-2.10 (26H, m, aliphatic H), 2.27 (2H, t, J = 7 Hz, CH_2CO), 2.70-4.00 (6H, m, 2x non-equivalent NCH_2 + CHN + CHOH), 4.10 (2H, q, J = 7 Hz, OCH_2), 4.36 (2H, AB m, CH_2Ph), 7.28 (5H, br.s, Ph).- MS: m/z = 473 (M^+ + 1 FABs). Further elution gave, after some fractions containing both diastereomers, the more polar diastereomer 13 (R_f 0.30) as an oil (1.3 g, 32%).- $C_{28}H_{44}N_2O_4$ (472.6).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 0.90-2.10 (26H, m, aliphatic H), 2.27 (2H, t, J = 7 Hz, CH_2CO), 2.60-3.90 (6H, m, 2x NCH_2 + CHN + CHOH), 4.10 (2H, q, J = 7 Hz, OCH_2), 4.34 (2H, AB m, CH_2Ph), 7.28 (5H, br.s, Ph).

Epimers 3 *and* 11

Ester 12 (0.85 g, 1.8 mmol), KOH (0.1 g, 1.8 mmol), methanol (10 ml) and water (5 ml) were stirred at room temp. for 2 h. The solvent was removed *in vacuo*, the residue acidified with 2 N HCl and extracted twice with ethyl acetate. After drying over $MgSO_4$ the combined extracts were concentrated *in vacuo* to give crude acid 14. Debenzylation of this acid (0.65 g, 1.5 mmol) with sodium in liquid ammonia was performed by an

Table: Pharmacological activities of BW245C analogues

Compd.	Inhibn. of ADP -induced human platelet aggregn. IC_{50} nM[a] (no. of experiments)	Relative Potency (PGE_1=1)	Blood Pressure Lowering Activity in Rat: Relative Potency[b] (PGI_2=1)	$t^1/_2$[c] (min.)
1[d]	4.0 ± 0.4 (10)	14	0.12 (n=4)	1.9 ± 0.3[e]
3	5.2 ± 1.0 (4)	10	0.01 (n=4)	1.6 ± 0.3
10	200 ± 60 (3)	0.3	I	
11	280 ± 25 (3)	0.1	I	

a IC_{50}, concentration required to reduce the aggregation to 50% of its control amplitude; values given are mean ± s.e.m. for (n) experiments. Potencies relative to PGE_1 are approximate. BW245C is approximately 8 and 0.2 times as potent as PGD_2 and PGI_2 respectively.

b Values given are relative to prostacyclin (PGI_2) in the same animal. I = inactive, relative potency < 0.001 the potency of PGI_2; Prostacyclin (0.25 ug kg^{-1} i.v.) caused a fall in blood pressure of 42 ± 5 mmHg (n=4).

c Half life of hypotensive effects at a dose that produces a decrease in diastolic blood pressure of 20 mmHg. Prostacyclin, $t^1/_2$ = 0.4 ± 0.1 min.

d The 15'-epimer of BW245C has IC_{50} = 195 ± 29 nM (n=3), 0.3 x PGE_1

e BW245C, $t1/_2$ = 6 ± 1 min at 5.0 ug kg^{-1} *i.v.*, blood pressure fall 35 ± 3 mmHg.

analogous procedure to that used for preparing acid **10**. The crude product was a yellow oil which was purified by flash chromatography on silica. Elution with chloroform-methanol (19:1) gave 290 mg (55%) of acid **3** as a white powder, m.p. 88-89°C (EtOAc-hexane).- $C_{19}H_{34}N_2O_4$ (354.5) Calc. C 64.4 H 9.67 N 7.9 Found C 64.2 H 9.81 N 7.7%.- ^{1}H-NMR [200 MHz, $(CD_3)_2SO$]: δ (ppm) = 0.80-1.85 (23H, m, aliphatic H), 2.17 (2H, t, J = 7 Hz, CH_2CO), 2.80-3.60 (8H, 2x NCH_2 + CHN + CHOH + CO_2H, 2H exchangeable), 6.18 (1H, s, NH, exchangeable).

Acid **11** was obtained as a syrup in 41% yield from ester **13**, *via* acid **15**, by an identical procedure. **11**: $C_{19}H_{34}N_2O_4$ (354.5).- ν max (film) 3360; 1700 (br) cm^{-1}.- ^{1}H-NMR [200 MHz, $(CD_3)_2SO$]: δ (ppm) = 0.80-1.80 (23H, m, aliphatic H), 2.20 (2H, t, J = 7 Hz, CH_2CO), 2.80-3.60 (7H, m, 2x NCH_2 + CHN + CHOH, 1H exchangeable), 6.20 (1H, s, NH, exchangeable).- MS: m/z = 355 (M^+ + 1, FABs).

Inhibition of Platelet Aggregation In Vitro

Human blood was freshly collected into siliconized (Siloclad: Clay Adams) plastic (Sterilin Ltd.) vessels containing trisodium citrate (3.15%; 0.1 volume with 0.9 volume blood) and centrifuged (200 g for 15 min) at room temp. The platelet-rich plasma (PRP) was withdrawn into plastic containers and kept at room temp. Inhibition of platelet aggregation was determined by a *Born*-type aggregometer as described[9] by incubating aliquots (0.5 ml) of the PRP for 1 min at 37°C with or without the prostaglandin analogue prior to addition of sufficient adenosine diphosphate (ADP) to just cause a non-reversing control aggregation.

Cardiovascular Actions in Rats

The blood pressure lowering ability of the prostaglandin analogues was determined in anaesthesised male Wistar rats; arterial pressure was recorded from a cannulated femoral artery as described[2].

References

1 A.G. Caldwell, C.J. Harris, R. Stepney, and N. Whittaker, J. Chem. Soc. Perkin Trans. *1*, 495 (1980).

2 P. Barraclough, A.G. Caldwell, C.J. Harris, W.P. Jackson, and B.J.R. Whittle, J. Chem. Soc. Perkin Trans. *1*, 1815 (1989) and references therein.

3 M.A. Orchard, J.M. Ritter, G.L. Shepherd, and P.J. Lewis, Br. J. Clin. Pharmac. *15*, 509 (1983).

4 P. Barraclough, A.G. Caldwell, C.J. Harris, and N. Whittaker, J. Chem. Soc. Perkin Trans. *1*, 2096 (1981).

5 N. Umino, T. Iwakuma, and N. Itoh, Tetrahedron Lett. *17*, 763 (1976).

6 D.N. Kursanov, Z.N. Parnes, and N.M. Loim, Synthesis, *1974*, 633.

7 A. Cervantes, A. Guzman, J.J. Bruno, Li-Feng Chang, and J.M. Muchowski, Rev. Soc. Quim. Mex. *30*, 63 (1986); C.A. *107*, 191640u (1987).

8 G.L. Bundy, D.R. Morton, D.C. Peterson, E.E. Nishizawa, and W.L. Miller, J. Med. Chem., *26*, 790 (1983).

9 B.J.R. Whittle, S. Moncada, and J.R. Vane, Prostaglandins, *16*, 373 (1978). [Ph820]