Synthesis and Platelet Aggregation Inhibiting Activity of Acid Side-chain Modified Hydantoin Prostaglandin Analogues

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A series of hydantoin prostaglandin analogues, in which the hexamethylene moiety of the acid side chain was replaced by other spacing groups possessing either ether, sulphide and/or olefin functionality, were prepared and evaluated for platelet aggregation inhibiting activity. The 4-thia analogue **13**[*)] proved to be the most potent inhibitor (ca. 22x PGE_1) and the 3-thia- and 3-oxa-analogues, **6** and **10** respectively, are approximately equipotent with BW245C (ca. 14x PGE_1). *Z*-olefinic analogues (e.g. **11**) were usually more potent than their *E*-isomers (e.g. **12**). Structure-activity relationships are discussed in detail.

Synthese und Plättchenaggregationshemmung von Hydantoin-Prostaglandin-Analogen, modifiziert in der Säureseitenkette

Eine Reihe Hydantoin-Prostaglandin-Analoger, in welcher der Hexamethylenteil der Säureseitenkette durch andere, Ether-, Sulfid- und/oder Olefin-enthaltende Gruppen ersetzt wird, wurde hergestellt und auf Plättchenaggregationshemmung untersucht. Das 4-Thia-analoge **13**[*)] ist der stärkste Hemmer (ca. 22 x PGE_1), die 3-Thia- und 3-Oxa-analogen **6** und **10** haben annähernd die gleiche Wirksamkeit wie BW245C (ca. 14 x PGE_1). *Z*-Olefinische Analoge (z.B. **11**) besitzen höhere Wirksamkeiten als ihre *E*-Isomeren (z.B. **12**). Struktur-Wirkung-Verhältnisse werden ausführlich diskutiert.

Prostaglandin D_2 (PGD_2) (**1**), is a potent inhibitor of human platelet aggregation, a vasodilator and it also exhibits a wide range of other pharmacological actions[1)]. However, whether these effects are mediated by a single PGD_2 receptor, previously classified as the DP receptor[2)], or by several subtypes of the DP receptor or other prostanoid receptors, is not yet known[3)].

The hydantoin prostaglandin analogue, BW245C **2**[4)], is also a potent inhibitor of human platelet aggregation and displays pronounced vasodepressor actions. Studies[5-7)] with selective DP receptor antagonists suggest that these effects are mediated through (DP)[2)] receptors.

In the vasculature, BW245C also acts on the DP receptor as well as another prostanoid receptor[7)], possibly a PGE_2 (EP_2)[2,5)] receptor. Additionally the PGE_1/PGI_2 (IP)[2)] receptor may also mediate some of the platelet effects of BW245C[6)]. More quantitative classification studies are at present hindered by the lack of selective antagonists for these two latter prostanoid receptors. Moreover, it is not yet known whether differences exist between DP receptors on human platelet membranes and in the human vasculature, and whether any differences could be exploited to develop a platelet-selective agent.

The search for a more platelet-selective analogue of BW245C which has reduced cardiovascular effects in man must therefore be somewhat empirical at this time.

In continuation of our detailed studies[8,9)] on the structure-activity relationships of hydantoin PGD_2 mimics, we now report the effects of modifying the acidic side chain of BW245C. It was of particular interest to know whether the introduction of oxygen or sulphur atoms and/or unsaturation into the hexamethylene chain of **2** would give rise to more potent and platelet selective agents. This study thus necessitated the synthesis and pharmacological evaluation of the analogues **3-20**[*)]. The ability of the hydantoin PG analogues to inhibit ADP-induced platelet aggregation was measured *in vitro* with human platelet rich plasma. Those analogues which proved to be more potent than PGE_1, were also tested for their hypotensive effects in anaesthetised rats.

Chemistry

BW245C **2**[10)], analogue **3**[11)] and analogue **20**[10)] were obtained by described methods. Hydantoins **4-19** were synthesized from the corresponding 2-substituted ethyl glycinates **21-36** by the five stage route (Scheme 1).

The intermediates were not routinely purified or characterized (other than by t.l.c.) since this was found to be unnecessary. Purification of the required PG analogues was achieved by washing the corresponding crude sodium salts with ether followed by column chromatography when required. The pharmacologically active less polar epimers **2-20** were then isolated from the diastereomeric mixtures (containing more polar epimers **41**) by prep. HPLC.

*) PG numbering (´omitted for convenience: 4-thia ≡ 4'-thia, *etc.*)

*) All analogues are racemic

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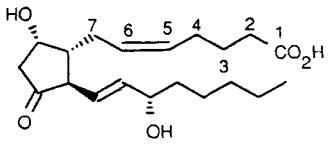

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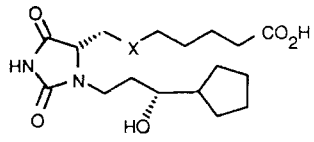
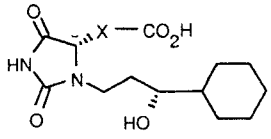
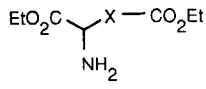


19 X=S
20 X=CH_2



X



2	BW245C	$(CH_2)_6$	
3		*Z*-$CH_2CH{:}CH(CH_2)_3$	
4		$(CH_2)_5$	21
5		$(CH_2)_7$	22
6		$(CH_2)_4SCH_2$	23
7		$(CH_2)_3SCH_2$	24
8		*Z*-$CH_2CH{:}CHCH_2SCH_2$	25
9		*E*-$CH_2CH{:}CHCH_2SCH_2$	26
10		$(CH_2)_4OCH_2$	27
11		*Z*-$CH_2CH{:}CHCH_2OCH_2$	28
12		*E*-$CH_2CH{:}CHCH_2OCH_2$	29
13		$(CH_2)_3S(CH_2)_2$	30
14		$(CH_2)_2S(CH_2)_2$	31
15		$(CH_2)_3O(CH_2)_2$	32
16		$(CH_2)_2S(CH_2)_3$	33
17		$(CH_2)_2O(CH_2)_3$	34
18		$(CH_2)_2S(CH_2)_4$	35
		$CH_2S(CH_2)_4$	36

Five different methods (**A-E**) were employed to prepare the ethyl glycinate precursors **21-36** as shown in Schemes 2-6. Suitable C-alkylation of diethylacetamidomalonate (DEAM, method **A**, Scheme 2) or benzylidene glycine ethyl ester (method **D**, Scheme 5) followed by acid hydrolysis of the C-alkylated intermediates gave glycinates **21**, **22**, **26-29**, and **32**. The milder hydrolysis conditions for method **D** avoided the problem of competing ether cleavage which was found to occur when method **A** was used to obtain glycinates **28** and **29**. These C-alkylations utilised the known bromides **42**[12], **43**[13], **45**[14], **59-61**[15], and chloride **44**, which was prepared by reaction of *E*-1,4-dichlorobut-2-ene with ethyl mercaptoacetate.

Glycinates **23-25** and **30** were obtained by reaction of the DEAM derivatives **50**[16], **51**[17], and **52**[18] with ethyl mercaptoacetate (or -propionate) and subsequent hydrolysis/re-esterification (method **B**) (Scheme 3). Similarly chloride **57**[19] was converted *via* malonate **58** to glycinate **34** (Scheme 4). S-Alkylation of cysteine or homocysteine methyl ester **62**[20] proved to be the simplest method (**E**, Scheme 6) of preparing glycinates **31**, **33**, **35**, and **36**.

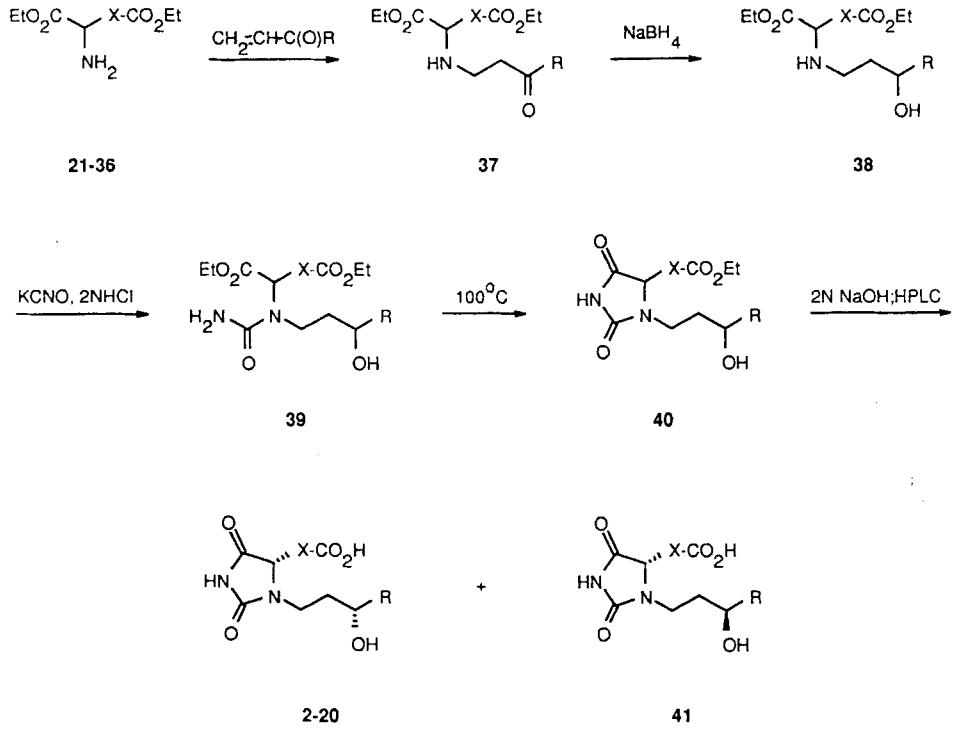
Many of the DEAM derivatives described above were used *in situ*, rigorous purification and characterization being performed only when t.l.c. and n.m.r. spectra indicated the presence of substantial by-products. Further details of the preparation and properties of the hydantoin analogues and glycinate intermediates are given in Tables 2 and 3, respectively, (Experim. Part).

Structure-activity relationships

The pharmacological properties of the BW245C analogues as inhibitors of human platelet aggregation and as hypotensive agents in the rat are given in Table 1. A number of saliant structure-activity points emerge from an analysis of the platelet data.

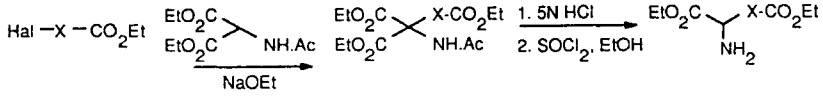
First it appears that a six atom array for the acid side chain linkage, X, is optimal. Thus either increasing or decreasing the hexamethylene spacer group of BW245C by

Scheme 1



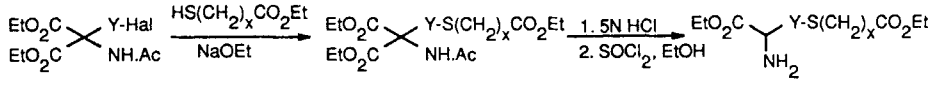
R = C_6H_{11} in all cases except for analogue **19** where R = C_5H_9

Scheme 2 (Method A)



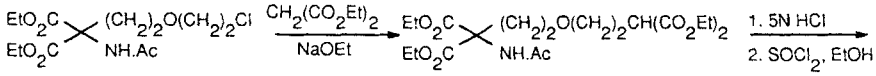
	Hal	X		
42	Br	$(CH_2)_5$	**46**	**21**
43	Br	$(CH_2)_7$	**47**	**22**
44	Cl	*E*-$CH_2CH{:}CHCH_2SCH_2$	**48**	**26**
45	Br	$(CH_2)_4OCH_2$	**49**	**27**

Scheme 3 (Method B)

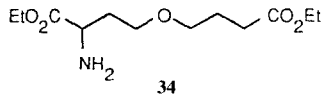


	Y-Hal		Y	x	
50	$(CH_2)_4Br$	**53**	$(CH_2)_4$	1	**23**
51	$(CH_2)_3Cl$	**54**	$(CH_2)_3$	1	**24**
51	$(CH_2)_3Cl$	**55**	$(CH_2)_3$	2	**30**
52	*Z*-$CH_2CH{:}CHCH_2Cl$	**56**	*Z*-$CH_2CH{:}CHCH_2$	1	**25**

Scheme 4 (Method C)



57 58



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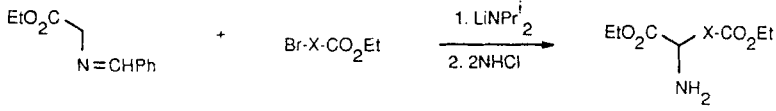
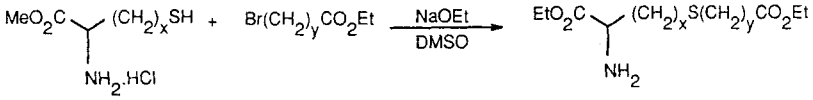
Scheme 5 (Method D)



	X	
59	*Z*-$CH_2CH{:}CHCH_2OCH_2$	28
60	*E*-$CH_2CH{:}CHCH_2OCH_2$	29
61	$(CH_2)_3O(CH_2)_2$	32

Scheme 6 (Method E)



	x		y	
62	2	64	2	31
62	2	65	3	33
62	2	66	4	35
63	1	66	4	36

CH_2 leads to lower platelet inhibitory properties. The relative potencies for the platelet inhibitory effects of **2**, **4**, and **5** indicate, however, that chain lengthening is better tolerated than chain shortening.

For the 3- and 4-thia analogues **6** and **13**, chain shortening by CH_2 also has a very detrimental effect on activity, as evidenced by the low potencies of analogues **7** and **14**. Analogue **7** is approximately 120 times less potent than **6** and BW245C (**2**), although the acid side chain of **7** is formally only ca. 0.5 Å shorter than the 'natural' side chain of **2**. Lengthening the side chain of the 5-thia analogue **16** also drastically reduces activity *cf.* potencies of **16** and **18**, which are 8x and 0.3x PGE_1, respectively.

Secondly the introduction of heteroatoms into the acid side chain seems to confer the more potent platelet inhibitory activity when the heteroatom is located in the 3- or 4-position. A comparison of the activities of the thia-analogues **6**, **13**, **16**, and **19** shows that the ranking order of potencies for replacement of a CH_2 by a S-atom is 4-S > 3-S > 5-S > 6-S. For the oxa-analogues **10**, **15**, and **17** the ranking is 3-O > 4-O > 5-O for replacement of CH_2 by an O-atom. A reduction of platelet inhibitory activity is observed when either the C-5 or C-6 atom is replaced by either S- or O-atoms. Thus the relative potencies of analogues **3**, **2**, **16**, **17**, and **19** indicate the following preference of 5,6 linking groups Z-CH=CH- > $-CH_2CH_2-$ > $-CH_2S-$ > $-CH_2O-$, ~ $-SCH_2-$.

The 5-oxa analogue of PGD_1 has also been reported[21] to be far less potent than PGD_1 as an anti-aggregating agent. The above findings may reflect the sensitivity of the C-5, C-6 region to perturbations of its normal electronic and conformational state. When the acid side chain does not contain olefinic functionality the sulphides are often found to be more potent than the corresponding ethers i.e. **13** > **15** and **16** > **17**. However, analogues **6** and **10** are approximately equipotent showing the 3-position to be less sensitive to heteroatom substitution. The overall ranking order of potencies for replacement of CH_2 by a heteroatom is there-

fore 4-S > 3-S, 3-O > 5-S > 4-O > 6-S, 5-O. For analogues possessing a 5,6 double bond, however, the ranking order is clearly different. A comparison of the potencies of analogues **8** *vs.* **11** and **9** *vs.* **12** shows that when a Z-5,6 double bond is present 3-O > 3-S, but for the *E*-olefin 3-S > 3-O.

Thirdly introduction of a Z-5,6 double bond into the acid side chain only led to more active analogues when heteroatoms were absent. Thus analogue **3** is more potent than **2** and this finding is consistent with the work of *Bundy*[21] who has shown that PGD_2 is much more potent than PGD_1. Ether **11** is slightly less potent than **10** and sulphide **8** is less active than analogue **6**. A Z-5,6 double bond does seem to be preferred to the *E*-olefinic functionality however. Z-olefins **8** and **11** are approximately 2 and 300 times more potent than their respective *E*-isomers **9** and **12**.

The potent platelet inhibitory activities of analogues possessing a Z-5,6-olefinic bond or a S- or O-atom at the 3- or 4-position may be related to the adoption of favourable conformations for these molecules, especially with regard to their acidic side chains. Thus when these analogues bind to the platelet receptor (probably the PGD_2 (DP) receptor) mediating their *anti*-aggregating effects their acidic side chains may more readily adopt conformations which give rise to potent ligand-receptor binding and expression of PGD_2 agonist responses. The geometries of these receptor-bound conformations are not known at present and may not be elucidated until X-ray studies on crystalline receptor-ligand complexes are performed. Nevertheless it is interesting to note the marked differences between the side chain conformations adopted by $PGF_2\alpha$*) in aqueous solution[22] and those of either $PGF_2\alpha$[22], BW245C[23] or PGE_2[24] in the crystal. In the solid state, the C3-C4 bond of BW245C and the C7-C8 bond of PGE_2 are in *gauche* conformations and the torsional angles for PGE_2 also indicate C-H eclipsed interactions around C-4 - C-5 and C-6 - C-7. These conformations may well be peculiar to the solid state. Nmr-studies[22], however, did not find any unusual conformational constraints present in the α-chain of $PGF_2\alpha$ in solution.

The solution conformations of $PGF_2\alpha$ (and possibly those of PGD_2) and the conformations of BW245C in the crystal thus bear little resemblance to the 'hairpin form'[25] seen in $PGF_2\alpha$ and PGE_2 solid-state structures where the two side chains are in proximity and specific alignment. Interestingly, a molecular modelling study[26] of over 200 PGI_2 analogues, suggests that IP receptor-bound PGI_2 exists in an elongated conformation (Fig. 1) very different from a 'hairpin form'. A similar analysis[27] performed on 80 BW245C and 22 PGD_2 agonists also found 'hairpin forms' disfavoured for DP receptor-bound PGD_2. Although a range of conformations seemed probable, elongated conformations having C-6 - C-9 distances longer than those of PGI_2, could be readily adopted by several potent PGD_2 mimics such as analogue **3** (Fig. 1). These models suggest that in the absence of other factors Z 5,6 olefinic PG's should be more potent DP receptor agonists (but less potent IP receptor agonists) than their *E*-isomers. PG side chains are highly flexible structures[22], however, and it remains to be seen which of the above conformations, if any, are adopted by the hydantoin analogues when in their receptor-bound state. Indeed the ability of BW245C to act at several prostanoid receptors may reflect an ability of the molecule to adopt several conformational states very readily. In addition, interaction of the side chain oxygen or sulphur lone pair may also contribute to binding of some ligands to the platelet receptor, raising the possibility that some analogues in this set bind in different modes. However, for the two most potent analogues, olefin **3** and sulphide **13**, the S lone pair at the 4-position of **13** may mimic the 5,6 double-bond of **3** and provide a similar electronic contribution in the same binding mode. At present we have no simple explanation of the SAR's observed, and the reasons for the complex effects of olefinic and heteroatom functionality on platelet activity remain obscure.

The most potent inhibitors of platelet aggregation identified in this study are the 4-thia, 3-thia and 3-oxa analogues **13**, **6**, and **10**, respectively. Hydantoins **13** and **3** are more potent (22x PGE_1) than BW245C (14x PGE_1). Analogues **6** and **10** are approximately equipotent as hypotensive agents. These two analogues also exhibited much weaker blood pressure lowering effects than BW245C in anaesthetised rats. However, further studies[27] in guinea pigs and dogs indicated there were only minor differences in the hypotensive effects of these agents and BW245C. Thus there is no evidence for an increased selectivity of platelet *vs.* cardiovascular effects for any of the analogues **3**, **6**, **10**, or **13**.

The discovery of BWA868C[5-7] as a potent and selective antagonist of the platelet inhibitory and cardiovascular actions of PGD_2 has stimulated further work towards a platelet selective PGD_2 mimic. In particular, *Collier* et al.[28] have speculated that a partial agonist at IP receptors may display platelet selectivity whereas the results of *Leff* [29] suggest that platelet selectivity will not be achievable at the DP receptor. In view of our present results this latter hypothesis has been studied thoroughly. In addition the many conformational possibilities relating to the present study have also led to an investigation of more conformationally constrained analogues. These studies will be reported elsewhere.

Experimental Part

Melting points: Kofler hot-stage instrument, uncorrected.- ^{1}H Nmr-spectra: Bruker HFX90, AM-200 (200 MHz) or WM-360 (360 Mz), TMS as internal standard; chem. shift in δ (ppm).- E.I. Mass spectra: A.E.I. MS 902 spectrometer, interfaced to a VG MULTISPEC data system at 70 eV. *Fast Atom Bombardment (FAB) mass spectra: Kratos MS 50 mass spectrometer*, RF magnet as described[8]. Thin layer chromatography (T.L.C.): Merck silica gel 60 F254; gravity column chromatography: Merck silica gel (60-120 mesh); flash chromatography: Merck silica gel (230-400 mesh). High performance liquid chromatography (HPLC): Bio-sil silica (20-44 μ). Separation of the hydantoin diastereomers was achieved with CH_2Cl_2-MeOH-acetic acid mixtures (e.g. 93:5:2).

*) PGD_2 is unstable; no crystal structure or studies of solution conformation have yet been reported.

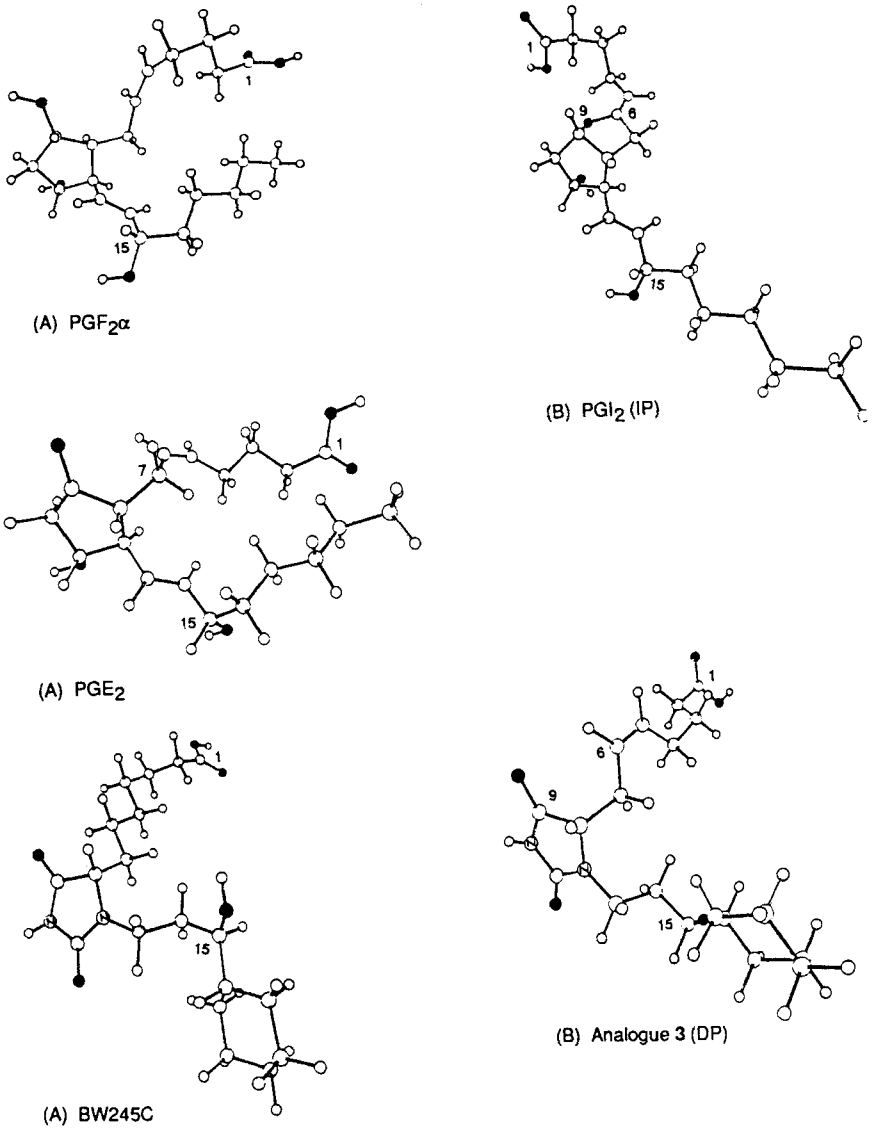


Figure 1 Spatial representations of (A) PG conformations in the solid state and (B) postulated PG conformations when bound to appropriate receptor. Geometrical parameters are given in references 22-27.

Conversion of ethyl glycinates to hydantoin PG analogues

(±)-(S,R*)7-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-5-oxa-heptanoic acid (17)*

Amine **34** (5.22 g, 0.02 mol) and cyclohexylvinyl ketone[10] (2.76 g, 0.02 mol) were mixed at 0°C and set aside at room temp. overnight giving ethyl 2-(3-cyclohexyl-3-oxopropylamino)-8-ethoxycarbonyl-5-oxaoctanoate [**37**, $X=(CH_2)_2O(CH_2)_3$] as an oil. A stirred solution of this ketone (7.90 g) in EtOH (100 ml) was treated dropwise at 0°C with $NaBH_4$ (0.75 g, 0.02 mol) in EtOH (70 ml), stirred at room temp. for 6 h, and then concentrated *in vacuo*. Water was added and the mixture was extracted with ether. The extracts were washed with brine, dried over $MgSO_4$ and evaporated to give 7.0 g of ethyl 2-(3-cyclohexyl-3-hydroxypropylamino)-8-ethoxycarbonyl-5-oxaoctanoate [**38**, $X=(CH_2)_2O(CH_2)_3$] as an oil consisting of two diastereomers, R_F 0.35; 0.40 (SiO_2; $CHCl_3$/MeOH, 50:1). To the foregoing crude amino-alcohol (6.9 g, 0.017 mol) dissolved in EtOH (40 ml) and 2N HCl (20 ml, 0.04 mol), a solution of KCNO (3.24 g, 0.04 mol) in water (10 ml) was added gradually with cooling and stirring, and the solution was left at room temp. overnight. Most of EtOH was evaporated, water was added, and the oil was extracted with ether. Evaporation of the washed and dried ethereal solution left an oil which was heated on a steam bath for 24 h to give the crude hydantoin ester [**40**, $X=(CH_2)_2O(CH_2)_3$], as a yellow oily mixture (6.6 g) of diastereomers R_F 0.40; 0.45 (SiO_2; $CHCl_3$/MeOH, 9:1), containing some impurities. This material was stirred with 2N aqueous NaOH (90 ml) at room temp. for 3 h. The insoluble non-acidic material was removed by washing with ether and the clear alkaline solution was acidified with 2N HCl. The acid was extracted with ethyl acetate, the combined extracts dried and evaporated. Chromatography of the residual crude product on silica and elution with $CHCl_3$/MeOH (19:1) gave 2.4 g (32%) of a mixture of **17** and **41** as a pale yellow syrup. The diastereomers were separated by HPLC: **17** (0.62 g, 8%) m.p. 111-112°C (ethyl acetate-hexane).- $C_{18}H_{30}N_2O_6$ (370.5) Calcd. C 58.4 H 8.16 N 7.56. Found C 58.5 H

Table 1: Pharmacological activities of BW245C analogues.

Compound	Inhibition of ADP-induced human platelet aggregn. IC_{50}, nM[a](n)	Relative Potency (PGE_1=1)	Blood Pressure Lowering activity in Rat Relative Potency[b] (PGI_2=1)
2	4.0±0.4 (10)	14	0.12 (n=4)
3	2.9±0.8 (4)	22	0.03 (n=4)
4	320±40 (2)	0.06	
5	7.6±1.5 (3)	7	0.08
6	4.7±1.1 (4)	12	0.02
7	280±40 (3)	0.1	
8	10.0±2.2 (3)	5	0.004
9	25±5 (3)	2	
10	4.2±0.9 (4)	14	0.03
11	5.3±1.2 (3)	9	0.02
12	600±200 (2)	0.03	
13	3.0±0.9 (4)	22	0.06 (n=4)
14	160±40 (2)	0.5	
15	16.0±3 (3)	3	
16	9.0±1.5 (3)	8	0.15
17	180±50 (2)	0.4	
18	200±60 (3)	0.3	
19	110±30 (2)	0.7	
20	8.5±2 (3)	8	0.07

IC_{50}, concentration reducing the aggregation to 50% of control amplitude: values 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. Relative potencies were confirmed by comparing the effects of groups of analogues (up to 5 per experiment) with BW245C and PGE_1 on the same batch of platelet rich plasma.

[b] Values are relative to prostacyclin in the same anaesthetised animal; number of experiments (n = 2 unless stated otherwise).

8.45 N 7.53.- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 0.95-2.32 (17 H, m, aliphatics), 2.47 (2H, t, J = 7 Hz, CH_2CO_2), 3.00-4.07 (7H, m, NCH_2, CHOH, CH_2OCH_2), 4.16 (1H, m, CHN).- m/z 371 (fab).

In a similar manner the following BW245C analogues were obtained:

3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinehexanoic acid (**4**),

3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidineoctanoic acid (**5**),

7-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-thiaheptanoic acid (**6**),

6-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-thiahexanoic acid (**7**),

7(Z)-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-thiahept-5,6-enoic acid (**8**),

7(E)-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-thiahept-5,6-enoic acid (**9**),

7-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-oxaheptanoic acid (**10**),

7(Z)-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-oxahept-5,6-enoic acid (**11**),

7(E)-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-3-oxahept-5,6-enoic acid (**12**),

7-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-4-thiaheptanoic acid (**13**),

6-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-4-thiahexanoic acid (**14**),

7-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-4-oxaheptanoic acid (**15**),

7-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-5-thiaheptanoic acid (**16**),

8-[3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-6-thiaoctanoic acid (**18**),

7-[3-(3-Cyclopentyl-3-hydroxypropyl)-2,5-dioxo-4-imidazolidinyl]-6-thiaheptanoic acid (**19**)

Details: Table 2.

Method **A**

(E)-Diethyl 2-acetamido-2-ethoxycarbonyl-7-thianon-4,5-enedioate (***48***)

Diethylacetamidomalonate (29.3 g, 0.13 mol) was added to a freshly prepared solution of sodium (3.10 g, 0.13 mol) in EtOH (120 ml). After stirring at room temp. for 15 min a solution of chloride **44** (28.1 g, 0.13 mol), in EtOH (20 ml) was added and the mixture then heated at reflux for 18 h. The cooled mixture was filtered, the filtrate evaporated, and water

Table 2: Preparation and Properties of Hydantoin PG Analogues

Compd.	Glycinate Intermediate	Yield (%)[a]	m.p.(°C)	Formula	Analysis calcd. (%) (Found)		
					C	H	N
4	**21**	75(15)	117-119	$C_{18}H_{30}N_2O_5$	61.0	8.53	7.90
				(354.5)	(60.9)	(8.41)	(8.03)
5	**22**	80(10)	90-92	$C_{20}H_{34}N_2O_5$	62.8	8.96	7.32
				(382.5)	(62.6)	(9.17)	(7.41)
6[b]	**23**	80(32)	glass	$C_{18}H_{30}N_2O_5S$	55.9	7.82	7.25[c]
			[104-108][c]	(386.5)	(55.7)[c]	(7.94)[c]	(7.16)[c]
7	**24**	52(16)	93-96	$C_{17}H_{28}N_2O_5S$	54.8	7.58	7.52
				(372.5)	(54.9)	(7.40)	(7.34)
8[b]	**25**	66(23)	117-118	$C_{18}H_{28}N_2O_5S$	56.2	7.34	7.29
				(384.5)	(56.4)	(7.44)	(7.16)
9	**26**	76(24)	glass	$C_{18}H_{28}N_2O_5S$	56.2	7.34	7.29
				(384.5)	(56.6)	(7.66)	(6.98)
10	**27**	78(18)	142-144	$C_{18}H_{30}N_2O_6$	58.4	8.16	7.56
				(370.4)	(58.3)	(8.09)	(7.48)
11[b]	**28**	82(34)	glass	$C_{18}H_{28}N_2O_6$	58.7	7.66	7.60
				(368.4)	(59.0)	(7.90)	(7.30)
12	**29**	68(10)	97-101	$C_{18}H_{28}N_2O_6$	58.7	7.66	7.60
				(368.4)	(58.7)	(7.62)	(7.50)
13	**30**	84(33)	101-103	$C_{18}H_{30}N_2O_5S$	55.9	7.82	7.25
				(386.5)	(56.1)	(8.00)	(7.09)
14[b]	**31**	73(25)	80-82	$C_{17}H_{28}N_2O_5S$	54.8	7.58	7.52
				(372.5)	(54.6)	(7.87)	(7.31)
15	**32**	70(16)	115-116	$C_{18}H_{30}N_2O_6$	58.4	8.16	7.56
				(370.4)	(58.3)	(8.02)	(7.34)
16	**33**	64(12)	84-86	$C_{18}H_{30}N_2O_5S$	55.9	7.82	7.25
				(386.5)	(56.0)	(8.12)	(7.08)
17[b]	**34**	32(8)	111-112	$C_{18}H_{30}N_2O_6$	58.4	8.16	7.56
				(370.4)	(58.5)	(8.45)	(7.53)
18	**35**	40(11)	70-73	$C_{19}H_{32}N_2O_5S$	57.0	8.05	6.99
				(400.5)	(57.3)	(8.21)	(6.80)
19[b]	**36**	7(1[d])	80-82	$C_{17}H_{28}N_2O_5S$	54.8	7.58	7.52
				(372.5)	(54.8)	(7.83)	(7.60)

[a] Overall yield of the pure, isolated mixture of hydantoin diastereomers (and analytically pure racemic less polar hydantoin diastereomer) obtained from the racemic glycinate intermediate. A quantitative reaction/purification sequence = 100% overall yield.

[b] ^{1}H-NMR Data (90 MHz, $CDCl_3$): Analogue **6**: δ = 0.80-2.0 (19 H, m, aliphatics), 2.66 (br.t, J = 7 Hz, CH_2S), 2.90-3.42 (4H, m, SCH_2CO, NCHHCHOH), 3.60-4.15 (2H, m, NCHH, CHN), 6.68 (2H, br.s, 2xOH, exchang.), 9.40 (1H, br.s, NH, exchang.).- Analogue **8**: δ = 0.80-2.0 (13 H, m, aliphatics), 2.67 (2H, m, $CH_2C{=}C$), 3.15 (2H, s, SCH_2CO), 3.2-3.5 (4H, m, NCHH, CHOH, $C{=}CCH_2S$), 3.6-3.9 (1H, NCHH), 4.03 (1H, br.t, J = 4 Hz, CHN), 5.4-5.8 (2H, m, CH=CH), 7-8 (2H, v.br. peak, 2 OH, exchang.), 10.2 (br.s, NH, exchang.).- Analogue **11**: δ = 0.80-1.95 (13 H, m, aliphatics), 2.71 (2H, m, $CH_2C{=}C$), 3.10-3.48 (2H, m, NCHH, CHOH), 3.60-4.20 (6H, m, NCHH, CH_2OCH_2, CHN), 5.50-5.94 (2H, m, CH=CH), 6.21 (2H, br.s, 2xOH, exchang.), 9.25 (1H, br.s, NH, exchang.).- Analogue **14**: δ = 0.90-2.0 (13 H, m, aliphatics), 2.08 (2H, m, CH_2CH_2S), 2.52-2.97 (6H, m, $CH_2SCH_2CH_2CO$), 3.0-4.0 (3H, NCH_2, -CHOH), 4.14 (1H, br.t, J = 4 Hz, CHN), 5.0-5.8 (2H, v.br. peak, 2xOH, exchang.).- Analogue **17**: δ =0.95-2.32 (17 H, m, aliphatics), 2.47 (2H, t, J = 7 Hz, CH_2CO), 3.00-4.07 (7H, NCH_2, -CHOH, CH_2OCH_2), 4.16 (1H, m, CHN).- Analogue **19**: δ = 0.92-1.95 (15 H, m, aliphatics), 2.32 (2H, br.t, J = 7 Hz, CH_2CO), 2.58 (2H, br.t, J = 7 Hz, SCH_2CH_2), 2.82-3.45 (2H, m, CHOH, NCHH), 3.04 (2H, t, J = 4 Hz, $CHCH_2S$), 3.73-4.07 (1H, m, NCHH), 4.23 (1H, br.t, J = 4 Hz, CHN), 6.2 (2H, v.br. peak, 2xOH, exchang.), 9.7 (1H, v.br. peak, NH, exchang.).

[c] refers to the more polar diastereomer of **6** i.e. **41**, $X{=}(CH_2)_4SCH_2$.

[d] low yield due to substantial decomposition during the thermolysis of **39** to **40**.

added to the residue. The mixture was extracted with ethyl acetate (2x), the extracts dried and the solvent removed *in vacuo*. The residual oil was purified by column chromatography (silica; chloroform) to give 41.7 g (80%) of **48** as a yellow oil.- $C_{17}H_{27}NO_7S$ (389.5).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.27, 1.30 (9H, 2xt, J = 7 Hz, 3xMe), 2.05 (3H, s, NCOMe), 3.16 (6H, m, $2xCH_2S$, CH_2C=C), 4.06-4.46 (6H, m, $3xOCH_2$), 5.32-5.57 (2H, m, CH=CH), 6.85 (1H, br.s, NH, exchang.).

In a similar manner were obtained diethyl 2-acetamido-2-ethoxycarbonyloctanedioate (**46**), diethyl 2-acetamido-2-ethoxycarbonyldecanedioate (**47**), and diethyl 2-acetamido-2-ethoxycarbonyl-7-oxanonanedioate (**49**).

(E)-Diethyl 2-amino-7-thianon-4,5-enedioate (26)

Triester **48** (40.0 g, 0.10 mol) and 3N HCl (400 ml; 1.2 mol) were stirred and heated at reflux for 4 h. The cooled mixture was evaporated *in vacuo* and the residue dried by azeotropic distillation with benzene-EtOH. The amino acid obtained was dissolved in dry ethanol (150 ml) and this solution was added over 1 h to a freshly prepared mixture obtained from $SOCl_2$ (25 ml, 0.34 mol) and dry ethanol (200 ml) at -20°C with stirring. After 1 h the resulting solution was allowed to stand at room temp. overnight and then heated at reflux for 1 h. Volatile material was removed *in vacuo* and the residual syrup poured onto ice-water. The pH of the mixture was adjusted to 11 by Na_2CO_3 and the oil extracted (3x) with ethyl acetate. The extracts were dried and evaporated to give an oil which was chromatographed on silica/Et_2O/CH_2Cl_2/EtOH (4:4:1) gave 19.8 g (70%) of **26**.- $C_{12}H_{21}NO_4S$ (275.3).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.29 (6H, t, J = 7 Hz, 2xMe), 1.53 (2H, br.s, NH_2, exchang.), 2.45 (2H, m, CH_2-C=C), 3.18 (2H, s, CH_2CO_2), 3.22 (2H, m, C=C CH_2S), 3.52 (1H, m, CHN), 4.20 (4H, q, J = 7 Hz, $2xOCH_2$), 5.42-5.70 (2H, m, CH=CH).- m/z (276, $(M+H)^+$, fab).

In a similar manner were obtained diethyl 2-aminooctanedioate (**21**), diethyl 2-aminodecanedioate (**22**), and diethyl 2-amino-7-oxanonanedioate (**27**). Details: Table 3.

Method B

Diethyl 2-acetamido-2-ethoxycarbonyl-7-thianonanedioate (53)

Ethyl mercaptoacetate (12.0 g, 0.10 mol) was added to a freshly prepared solution of sodium (2.30 g, 0.10 mol) in dry EtOH (130 ml). The solution was stirred 15 min and then added over 10 min to a stirred solution of diethyl (4-bromobutyl)acetamidomalonate (**50**)[16] (35.2 g, 0.10 mol) in dry EtOH (150 ml). Stirring was continued for 24 h at room temp., the mixture diluted with water, and then extracted with chloroform (2x). The extracts were washed with brine, and filtered through a small silica pad. Evaporation of the filtrate and chromatography of the residue on silica/chloroform gave 28 g (72%) of a colourless gum, **53**.- $C_{17}H_{29}NO_7S$ (391.3).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.26, 1.28 (9H, 2xt, J = 7 Hz, 3xMe), 1.50-1.90 (4H, m, CH_2CH_2), 2.05 (3H, s, NCOMe), 2.63 (4H, br.t, J = 7 Hz, CH_2S, CH_2C), 3.20 (2H, s, SCH_2CO), 4.05-4.45 (6H, m, $3xOCH_2$), 6.85 (1H, br.s, NH, exchang.).

In a similar manner were obtained diethyl 2-acetamido-2-ethoxycarbonyl-6-thiaoctanedioate (**54**), diethyl 2-acetamido-2-ethoxycarbonyl-6-thianonanedioate (**55**), and (Z)-diethyl 2-acetamido-2-ethoxycarbonyl-7-thianon-4,5-enedioate (**56**).

Diethyl 2-amino-7-thianonanedioate (23)

Triester **53** (25.0 g, 0.06 mol) and 3N HCl (300 ml, 0.9 mol) were stirred and heated at reflux for 3 h. The cooled mixture was evaporated, the residue azeotropically dried by addition and evaporation of ethanol (3x), to give a colourless gum. This substance was dissolved in dry EtOH (100 ml) and the solution added over 0.5 h to a stirred mixture of $SOCl_2$ (20 ml, 0.28 mol) and dry EtOH (120 ml) at -20°C. The mixture was stirred at room temp. overnight and then heated at reflux for 1 h. After cooling the solution was poured onto ice, adusted to pH 12 with Na_2CO_3 and extracted (3x) with $CHCl_3$. The extracts were dried, evaporated, and the residual oil was chromatographed on silica/Et_2O-CH_2Cl_2-EtOH (4:4:1) to give 12.5 g (70%) of a pale yellow oil **23**.- $C_{12}H_{23}NO_4S$ (277.4).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.29 (6H, t, J = 7 Hz, 2xMe), 1.50-1.90 (6H, m, $3xCH_2$), 1.60 (2H, s, NH_2, exchang.), 2.67 (2H, br.t, J = 7 Hz, $CH_2\underline{CH_2}S$), 3.23 (2H, s, SCH_2CO_2), 3.42 (1H, m, CHN), 4.22 (4H, q, J = 7 Hz, 2 CO_2CH_2).- m/z (278, $(M+H)^+$, fab).

In a similar manner were obtained diethyl 2-amino-6-thiaoctanedioate (**24**), diethyl 2-amino-6-thianonanedioate (**30**), and (Z)-diethyl 2-amino-7-thianon-4,5-enedioate (**25**). Details: Table 3.

Method C

Diethyl 2-acetamido-2,8-di(ethoxycarbonyl)-5-oxanonanedioate (58)

Diethyl malonate (10.5 g, 0.065 mol) was added to a freshly prepared solution of sodium (1.5 g, 0.065 mol) in EtOH (200 ml). The solution was allowed to stand at room temp. for 15 min and then a solution of 2-(2-chloroethoxy-ethyl)-acetamidomalonate **57**[19] (20.0 g, 0.062 mol) in EtOH (60 ml) and NaI (9.30 g, 0.062 mol) added consecutively. The mixture was heated at reflux for 24 h, cooled and evaporated. Water was added to the residue and the mixture was extracted with ether (2x). The extracts were dried, the solvent was removed *in vacuo*, and the residue chromatographed on silica/ether to give 15.1 g (55%) of an oil **58**.- $C_{20}H_{33}NO_{10}$ (447.4).- ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.27 (12 H, t, J = 7 Hz, 4xMe), 2.05 (3H, s, N-COMe), 2.05-2.23 (4H, m, $2xO\text{-}CH_2\text{-}C\underline{H_2}$), 3.33-3.60 (4H, m, CH_2OCH_2), 4.10-4.31 (8H, m, $4xCO_2CH_2$), 4.65 (1H, m, O_2CCHCO_2), 6.59 (1H, br.peak, NH, exchang.).- $(M+H)^+$ m/z (448, fab).

Diethyl 2-amino-5-oxanonanedioate (34)

Tetraester **58** (14.0 g, 0.03 mol), conc. HCl (110 ml, 1.2 mol) and water (200 ml) were stirred and heated at reflux for 5 h. The cooled mixture was evaporated to dryness and the last traces of water removed by azeotropic distillation with benzene. The residual amino acid was dissolved in dry EtOH (25 ml) and the solution added dropwise with stirring to a freshly prepared mixture of $SOCl_2$ (20 g, 0.17 mol) and dry EtOH (125 ml) at -30°C. After stirring at this temp. for 1 h, and at room temp. overnight, the mixture was heated at reflux for 2 h. The resulting solution was cooled, the volatile material was removed *in vacuo* and the residue poured onto ice-water. The mixture was brought to pH 11 by Na_2CO_3, the aqueous layer saturated with salt, and the liberated oil extracted with ethyl acetate (4x). The extracts were dried over Na_2SO_4, evaporated and the residue distilled under reduced pressure to give 5.3 g (65%) of a pale yellow oil **34**, b.p. 102-108°C/0.03 mm.- $C_{12}H_{23}NO_5$ (261.3).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.20, 1.21 (6H, 2xt, J = 7 Hz, 2xMe), 1.63 (2H, br.s, NH_2, exchang.), 1.82-2.32 (6H, m, CH_2CO_2, $2xCH_2$), 3.31-3.59 (5H, m, $2xOCH_2$, CH), 4.03, 4.17 (m, $2xCO_2CH_2C$).- m/z 262 ($(M+H)^+$, fab).

Method D

(E)-Diethyl 2-amino-7-oxanon-4,5-enedioate (29)

A solution of lithium diisopropylamide in dry THF (200 ml) was prepared from diisopropylamine (4.00 g, 0.04 mol) and butyl lithium (24.0 ml of 1.62M, 0.04 mol) in hexane. Hexamethylphosphoramide (60 ml) was added and the stirred solution cooled to -78°C. A solution of glycine benzylidene ethyl ester[30] (8.00 g, 0.04 mol) in a little dry THF was added slowly and the mixture stirred at -78°C for 30 min. *(E)*-Ethyl (4-bromobut-2,3-enyloxy)acetate (**60**)[15] (9.48 g, 0.04 mol) in a little dry THF was then added and the resulting solution was allowed to warm to room temp. and then stirred for 18 h. Most of the solvent was removed *in vacuo* and the

Table 3: Preparation and Properties of Ethyl Glycinates

Amine	Method: Intermediates	Yield(s) %	Formula	Physical data[e,f,g,h]
21	A: **42**[12]), **46**	64[a]	$C_{12}H_{23}NO_4$ (245.3)	b.p. 99-101°C/0.02mm, NMR
22	A: **43**[13]), **47**	50[a]	$C_{14}H_{27}NO_4$ (273.4)	b.p. 123-126°C/0.04mm, Anal
23	B: **50**[16]), **53**	70[b], 72[c]	$C_{12}H_{23}NO_4S$ (277.4)	NMR, MS
24	B: **51**[17]), **54**	40[a]	$C_{11}H_{21}NO_4S$ (263.4)	b.p. 135-8°C/0.01mm, Anal, MS
25	B: **52**[18]), **56**	45[a]	$C_{12}H_{21}NO_4S$ (275.4)	NMR, MS
26	A: **44**, **48**	70[b], 80[c]	$C_{12}H_{21}NO_4S$ (275.4)	NMR, MS
27	A: **45**[14]), **49**	35[a]	$C_{12}H_{23}NO_5$ (261.3)	b.p. 118-121°C/0.005mm, NMR, MS
28	D: **59**[15]), BGE[d]	40[b]	$C_{12}H_{21}NO_5$ (259.3)	NMR, MS
29	D: **60**[15]), BGE[d]	40[b]	$C_{12}H_{21}NO_5$ (259.3)	b.p. 120-122°C/0.005mm Anal, NMR
30	B: **51**[17]), **55**	36[a]	$C_{12}H_{23}NO_4S$ (277.4)	b.p. 133-136°C/0.02mm Anal, MS
31	E: **62**[20]), **64**	52[b]	$C_{11}H_{21}NO_4S$ (263.4)	b.p. 130-133°C/0.04mm NMR, MS
32	D: **61**[15]), BGE	60[b]	$C_{12}H_{23}NO_5$ (261.3)	b.p. 108-112°C/0.03mm, Anal, MS
33	E: **62**[20]), **65**	68[b]	$C_{12}H_{23}NO_4S$ (277.4)	b.p. 140-144°C/0.05mm, NMR, MS
34	C: **57**[19]), **58**	65[b], 55[c]	$C_{12}H_{23}NO_5$ (261.3)	b.p. 102-108°C/0.03mm, NMR, MS
35	E: **62**[20]), **66**	34[b]	$C_{13}H_{25}NO_4S$ (291.4)	b.p. 140-144°C/0.02mm, Anal, MS
36	E: **63**, **66**	48[b]	$C_{12}H_{23}NO_4S$ (277.4)	b.p. 130-134°C/0.02mm, NMR, MS

[a] Overall yield for the preparation of pure, isolated glycinate from the first intermediate in the sequence. The second intermediate was used *in situ*. Amine **21**, for example, was obtained in 64% overall yield from bromide **42**. Amide **46** was used as a crude product.

[b] Yield for the preparation of pure, isolated glycinate from the last intermediate in the sequence which was purified and isolated. Amine **23**, for example, was obtained in 70% yield from amide **53**.

[c] Yield for the preparation of the last intermediate. Amide **53**, for example, was obtained in 72% yield from bromide **50**.

[d] BGE is N-Benzylidene glycine ethyl ester[30]).

[e] Column chromatography was routinely used to purify the glycinates. Although several of these amines were further purified by distillation low yields of the products, as oils, were often obtained; substantial amounts of non-distillable residues remained in the distillation flask. The glycinates could be stored satisfactorily at -20°C for up to one month. After this time these oils had partly solidified; the solids were found to contain the diketopiperazine derivatives and intractable polymeric material.

[f] ^{1}H-NMR data (90 MHz, $CDCl_3$): **21**, δ = 1.24, 1.27 (6H, 2xt, J = 7 Hz, 2xMe), 1.40-1.80 (8H, m, 4xCH_2), 1.94 (2H, br.s, NH_2, exchang.), 2.28 (2H, br.t, J = 7 Hz, CH_2CO_2), 3.42 (1H, m, CHN), 3.90-4.30 (4H, m, 2xOCH_2).- **23**, see Exp. part.- **25**, δ = 1.28 (6H, t, J = 7 Hz, 2xMe), 1.61 (2H, s, NH_2, exchang.), 2.49 (2H, m, CH_2C=C), 3.19 (2H, s, CH_2CO), 3.24-3.62 (3H, m, CH_2S, CHN), 4.20 (4H, q, J = 7 Hz, 2xOCH_2), 5.61 (2H, m, CH=CH), **26**, see Exp. part.- **27**, δ = 1.29 (6H, t, J = 7 Hz, 2xMe), 1.45-1.90 (8H, m, aliphatics, NH_2, 2H, exchang.), 3.54 (3H, m, OCH_2, CHN), 4.05 (2H, s, CH_2CO), 4.18, 4.22 (4H, 2xq, J = 7 Hz, 2xCO_2CH_2).- **28**, δ = 1.27 (6H, t, J = 7 Hz, 2xMe), 1.62 (2H, br.s, NH_2, exchang.), 2.47 (2H, m, CH_2C=C), 3.51 (1H, m, CHN), 4.00-4.40 (8H, m, 2xCO_2CH_2, CH_2OCH_2CO), 5.70 (2H, m, CH=CH).- **29**, see Exp. part.- **31**, δ = 1.19, 1.20 (6H, 2xt, J = 7 Hz, 2xMe), 1.46 (2H, s, NH_2, exchang.), 2.60 (2H, m, CHNC$\underline{H}_2$), 2.27-2.66 (6H, m, $CH_2SCH_2CH_2CO$), 3.48 (1H, m, CHN), 4.06, 4.11 (4H, 2xq, J = 7 Hz, 2xOCH_2).- **33**, δ = 1.18, 1.20 (6H, 2xt, J = 7 Hz, 2xMe), 1.50 (2H, s, NH_2, exchang.), 1.52-1.99 (4H, m, 2xC$\underline{H}_2$-CH_2-S), 2.27-2.66 (6H, m, CH_2SCH_2, CH_2CO), 3.48 (1H, m, CHN), 4.05, 4.10 (4H, 2xq, J = 7 Hz, 2xOCH_2).- **34**, δ = 1.20, 1.21 (6H, 2xt, J = 7 Hz, 2xMe), 1.63 (2H, br.s, NH_2, exchang.), 1.82-2.32 (6H, m, CH_2CH_2CO, CHNC$\underline{H}_2$), 3.31-3.59 (5H, m, CH_2OCH_2, CHN), 4.03-4.17 (4H, m, 2xCO_2CH_2).- **36**, δ = 1.14, 1.18 (6H, 2xt, J = 7 Hz, 2xMe), 1.58 (4H, m, aliphatics), 1.84 (2H, br.s, NH_2, exchang.), 2.21 (2H, t, J = 7 Hz, CH_2CO), 2.48-2.78 (4H, m, CH_2SCH_2), 3.53 (1H, m, CHN), 4.06 (4H, m, 2xOCH_2).

[g] Mass Spectral (MS) data (fab) The following $(M+H)^+$ ions of high intensity were observed: **23**: m/z 278; **24**: m/z 264; **25**: m/z 276; **26**: m/z 276; **27**: m/z 262; **28**: m/z 260; **30**: m/z 278; **31**: m/z 264; **32**: m/z 262; **33**: m/z 278; **34**: m/z 262; **35**: m/z 292; **36**: m/z 278.

[h] Analytical data: **22**: Calcd. C 61.5 H 9.96 N 5.12 Found C 61.6 H 10.1 N 5.05; **24**: Calcd. C 50.2 H 8.04 N 5.32 Found C 50.5 H 7.95 N 5.09; **29**: see Exp. part; **30**: Calcd. C 52.0 H 8.36 N 5.05 Found C 52.3 H 8.68 N 4.80; **32**: Calcd. C 55.2 H 8.87 N 5.36 Found C 54.9 H 9.08 N 5.10; **35**: Calcd. C 53.6 H 8.65 N 4.81 Found C 53.9 H 8.89 N 4.54.

residue was diluted with ether and washed with aqueous NH_4Cl. The organic extract was dried, the solvent removed *in vacuo* and the residual oil stirred with 0.5N HCl (200 ml) for 1 h. The resulting suspension was thoroughly extracted with ether, the separated aqueous phase made alkaline (pH 11-12) with solid Na_2CO_3, and the mixture extracted with $CHCl_3$. The extracts were dried and evaporated to give a yellow syrup. This material was purified by column chromatography on silica/chloroform-ethanol (9:1) to give 4.14 g (40%) of **29** as a pale yellow oil. Distillation under reduced pressure gave an analytical sample of **29**, a colourless oil, b.p. 121.5°/0.005 mm.- $C_{12}H_{21}NO_5$ (259.3) Calcd. C 55.6 H 8.16 N 5.40 Found C 55.8 H 8.22 N 5.19.- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.28 (6H, t, J = 7 Hz, 2xMe), 1.55 (2H, br.s, NH_2, exchang.), 2.50 (2H, m, CH_2C=C), 3.53 (1H, m, CHN), 4.00-4.43 (8H, m, 2xCO_2CH_2, CH_2OCH_2CO), 5.60-5.85 (2H, m, CH=CH).

In a similar manner were obtained (Z)-diethyl 2-amino 7-oxanon-4,5-enedioate (**28**) and diethyl 2-amino 6-oxanonanedioate (**32**). Details Table 3.

Method ***E***

S-alkylation of cysteine derivatives

*Diethyl 2-amino-4-thianonanedioate (**36**)*

D,L-Cysteine methyl ester hydrochloride **63** (17.2 g, 0.10 mol) was added to a freshly prepared solution of sodium (4.60 g, 0.20 mol) in dry ethanol (320 ml). The mixture was stirred for 15 min, evaporated and the last traces of EtOH were removed under high vacuum. The residual ethyl sodiocysteinate was dissolved in dry DMSO (200 ml) and then ethyl 5-bromovalerate (**66**) (21.0 g, 0.10 mol) was added in a single portion. The reaction mixture was stirred at room temp. overnight and then poured onto ice-water containing NaH_2PO_4 (1 g). The mixture was extracted with ether, the extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent *in vacuo* and flash distillation gave 13.2 g (48%) of a pale yellow oil, b.p. 130-134°C/0.02 mm **36**.- $C_{12}H_{23}NO_4S$ (277.4).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.14, 1.18 (6H, 2q, J = 7 Hz, 2Me), 1.58 (4H, m, 2xCH_2), 1.84 (2H, br.s, NH_2, exchang.), 2.21 (2H, t, J = 7 Hz, CH_2CO_2), 2.48-3.52 (4H, m, CH_2SCH_2), 3.52 (1H, m, CHN), 4.06 (4H, m, 2xOCH_2).- m/z (278 $(M+H)^+$).

In a similar manner were obtained diethyl-2-amino-5-thiaoctanedioate (**31**), diethyl-2-amino-5-thianonanedioate (**33**), and diethyl-2-amino-5-thiadecanedioate (**35**). Details: Table 3.

*(E)-Ethyl 7-Chloro-3-thiahept-5,6-enoate (**44**)*

Ethyl mercaptoacetate (24.0 g, 0.20 mol) was added to a freshly prepared solution of sodium (4.60 g, 0.20 mol) in dry EtOH (300 ml). The solution was stirred 15 min and then added over 2 h to (*E*)-1,4-dichlorobut-2-ene (75.0 g, 0.60 mol) with vigorous stirring under N_2. Stirring was continued for 60 h at room temp. and then the mixture was filtered. Evaporation of the filtrate and distillation of the residue gave, after removal of recovered (*E*)-1,4-dichlorobut-2-ene, 28.2 g (68%) of a colourless, unstable oil **44**, b.p. 90-93°C/0.05 mm.- $C_8H_{13}ClSO_2$ (208.7).- ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.30 (3H, t, J = 7 Hz, Me), 3.15 (2H, s, SCH_2CO), 3.18-3.35 (2H, m, CH-C$\underline{H}_2$S), 4.00-4.38 (4H, m, CH_2Cl, OCH_2), 5.66-5.90 (2H, m, CH=CH).

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[8] 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 following bolus intravenous administration was determined in anaesthesised male Wistar rats; arterial pressure was recorded from a cannulated femoral artery as described[8].

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[Ph 28]