Heterocyclic Prostaglandin Analogues. Part 2.[1] Hydantoins and Other Imidazole Analogues

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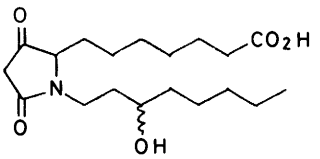
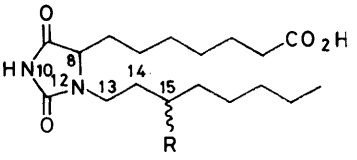
The stable hydantoin prostaglandin analogues (2b) and (3b) have been synthesised as racemic compounds. The less polar diastereoisomer of (2b) is a potent inhibitor of platelet aggregation in human platelet-rich plasma and its cyclohexyl analogue (22, R = C_6H_{11}) has *ca.* 14 times the potency of prostaglandin E_1 in this test coupled with selectivity of biological action. Other structural modifications such as introduction of a 15-methyl group and insertion of the *m*-phenylene or *m*-oxaphenylene moieties into the acid side-chain of (2b) led to a reduction in anti-aggregatory potency. Synthesis of the imidazole (41) is described.

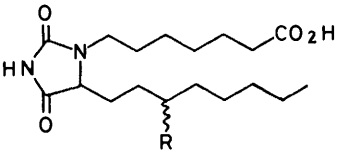
THE striking and diverse biological activities of the prostaglandins are well known. However, development of effective therapeutic agents based on them necessitates the discovery of compounds which have selectivity of biological action. In a search for such compounds, a group of pyrrolidinedione prostaglandin analogues was developed in our laboratories [1] and has also been reported by other groups.[2] In our hands, compound (1) was a moderately active inhibitor of platelet aggregation in human platelet-rich plasma but, because of its tendency to form an anhydrodimer spontaneously,[1] it could only be regarded as an initial lead to a potentially useful therapeutic agent. For this reason, hydantoins (2b) and (3b) which may be designated as 10,12-diaza- and 8,10-diaza-prostaglandins,† and numerous analogues of (2b) have now been investigated.‡



(1)



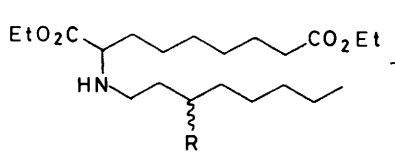
(2) a; R = H
b; R = OH



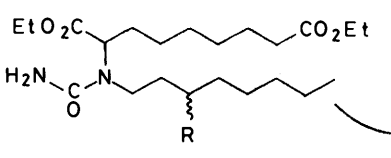
(3) a; R = H
b; R = OH

To assess the utility of the α-amino-ester–cyanic acid reaction for the synthesis of hydantoins of types (2) and (3), the amino-diester (4a) [1,2a] was treated with excess of cyanic acid in aqueous alcohol at room temperature overnight. Work-up gave a mixture of the hydantoic ester (5a) with the hydantoin (6a) but heating of this mixture at 100 °C for a few hours brought about complete conversion into the hydantoin in good yield.[3] Hydrolysis of the ester function with aqueous alkali then gave the hydantoin (2a) as a crystalline solid. Similarly, the intermediate (7a) afforded the isomeric crystalline hydantoin (3a).§

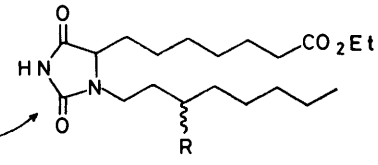
Reaction of the 2-(3-hydroxyoctyl)amino-diester [1,2] (4b) with cyanic acid also proceeded well under the same conditions without prior protection of the hydroxy-function. The resulting hydantoin (6b), like its precursors (4c and b), was a gum not easily purified, but treatment of the crude product with aqueous alkali at room temperature simultaneously brought about purification ¶ and hydrolysis of the ester, to give the hydantoin (2b). Similarly, the oxo-octyl intermediate (4c) could be converted, although in poor yield, into the hydantoin (6c) and thence, by hydrolysis and reduction, into the same hydroxy-compound (2b). Compound (2b) was an oily mixture of diastereoisomers readily distinguishable by t.l.c. Separation by h.p.l.c. on silica afforded the individual isomers as crystalline solids,



(4) a; R = H
b; R = OH
c; R = O



(5) a; R = H
b; R = OH

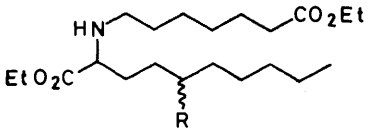


(6) a; R = H
b; R = OH
c; R = O

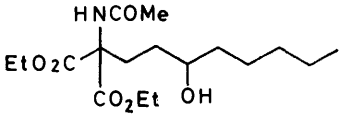
† Prostanoic acid numbering is used throughout the Discussion.
‡ All the analogues described herein were synthesised as racemic compounds.

§ Smith *et al.*[4] have recently prepared (3a) but describe it as a yellow oil.
¶ The hydantoin (6b) alone, by virtue of its acidic nucleus, passed from the oily into the aqueous phase.

stable in neutral or acid solution and slowly interconvertible by base. It was also possible to separate the intermediate (4b) into its component diastereoisomers, since only one of them gave a crystalline hydrochloride, and to convert each one by the foregoing reaction sequence into the corresponding hydantoin (2b) diastereoisomer. In the final ester hydrolysis step, the use of only a small excess of alkali avoided stereochemical equilibration at C-8.



(7) a; R = H
b; R = OH



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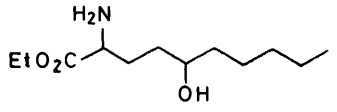
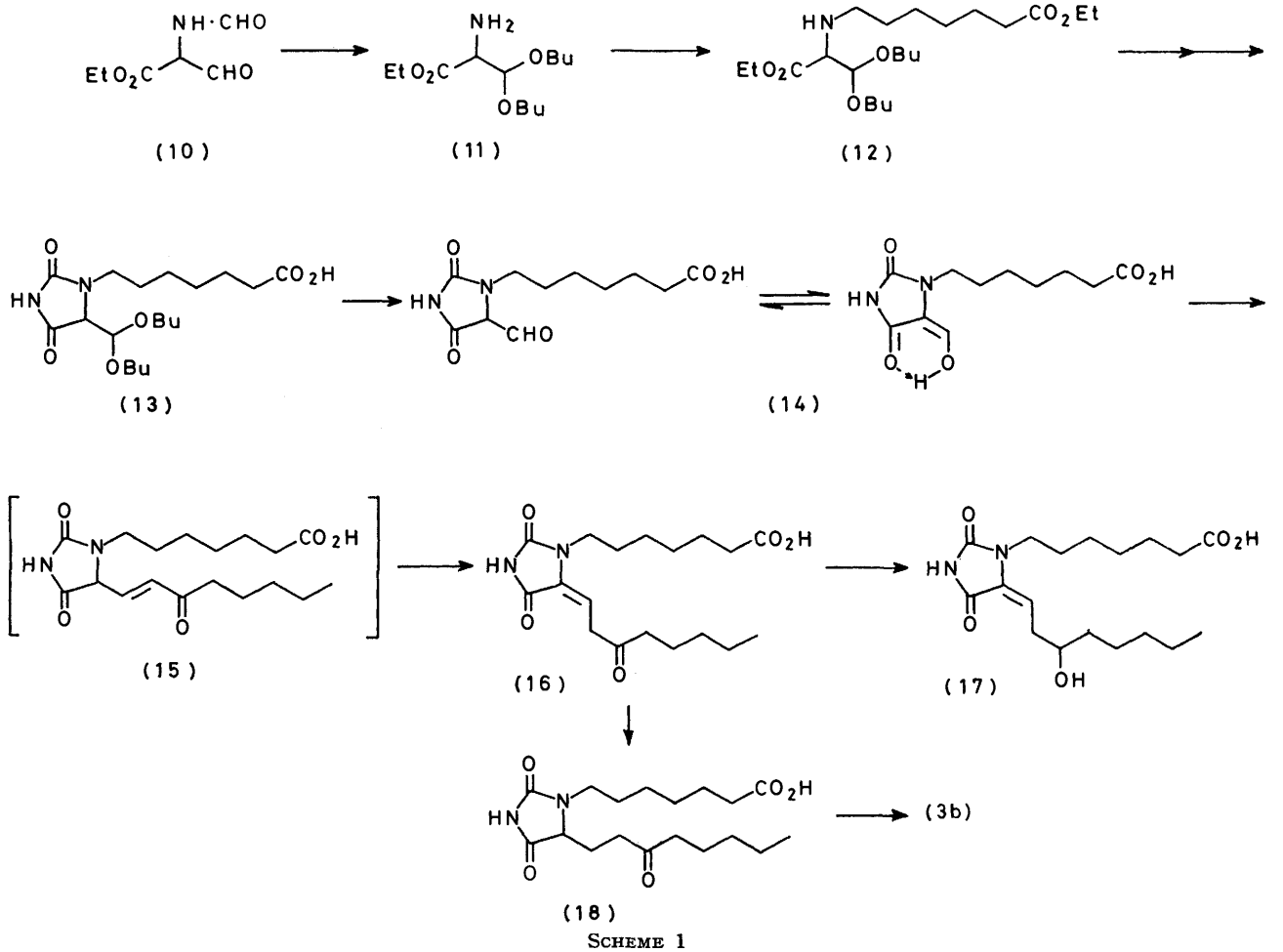


(9)

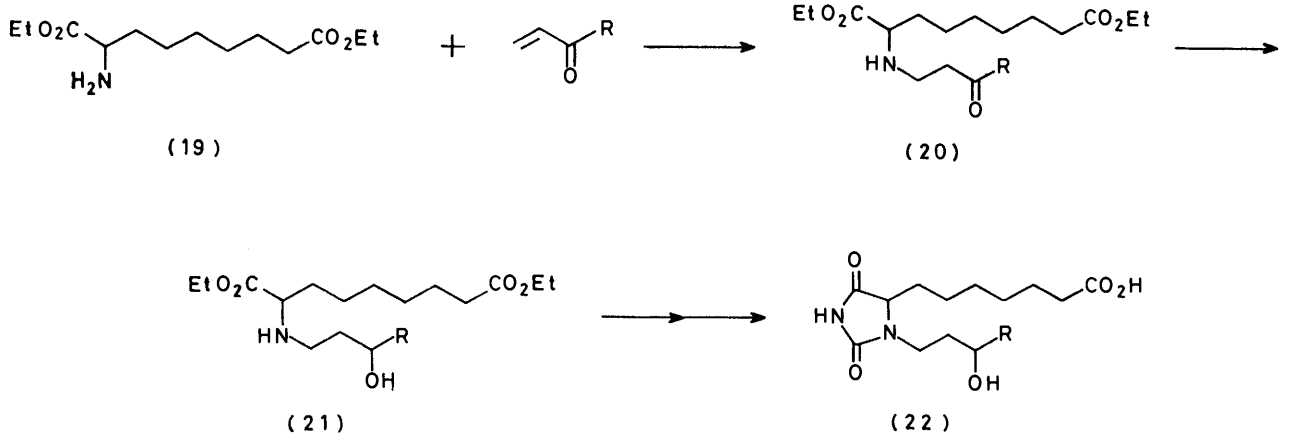
For the synthesis of hydantoin (3b), preparation of the required intermediate (7b) was attempted *via* compounds (8) and (9). Base-catalysed Michael addition of diethyl acetamidomalonate to oct-1-en-3-one followed by reduction of the adduct with sodium borohydride in ethanol at 0 °C gave the alcohol (8); surprisingly, however, subjection of (8) to the usual hydrolysis–decarboxylation conditions,[5] with subsequent exposure to ethanolic hydrogen chloride gave a mixture of compounds from which the amino-ester (9) was not isolable. An alternative approach was therefore investigated (Scheme 1).

N,2-Diformylglycine ethyl ester[6] (10), obtained by an improved procedure, was converted[7] into the acetal (11) which was heated with ethyl 7-bromoheptanoate in the absence of solvent to give the disubstituted glycine ester (12) in good yield. Reaction of (12) with cyanic acid followed by ester hydrolysis yielded hydantoin (13) but hydrolysis of the acetal moiety of (13) using conventional methods did not proceed in good yield. Ultimately it was found that the acetal (13) was readily soluble in concentrated hydrochloric acid to give a



SCHEME 1

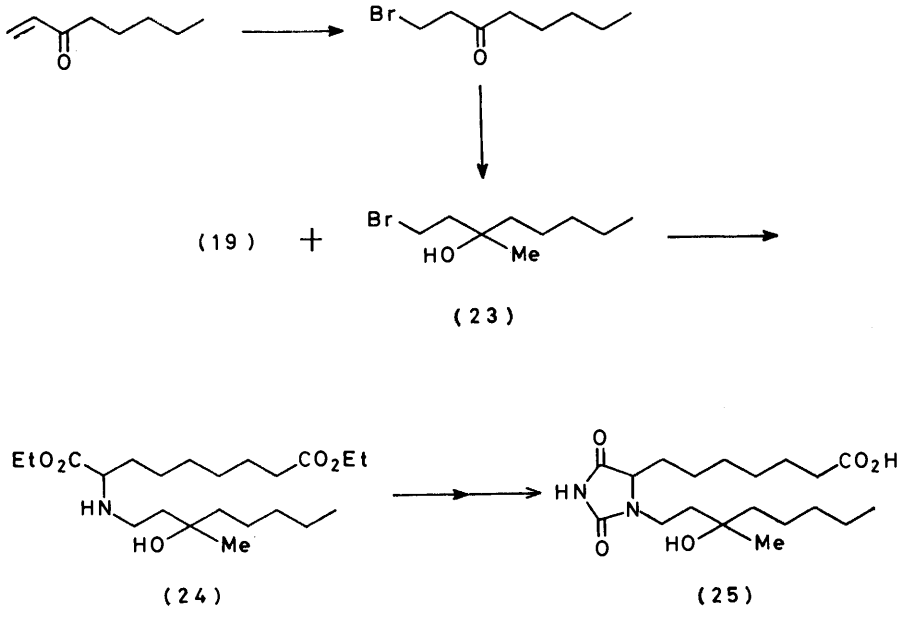
solution from which the desired masked aldehyde (14) soon crystallised out in excellent yield. ^{1}H N.m.r. measurements on this high-melting solid detected only the hydroxymethylene form in deuteriated dimethyl sulphoxide; nevertheless it underwent a Wittig reaction with 2-oxoheptylidenetriphenylphosphorane at 100 °C in the presence of a little benzene. The isolated product had only one vinyl proton, δ 5.72 (1 H, t, *J* 7.1 Hz), coupled to methylene adjacent to carbonyl, δ 3.93 (2 H, d), and a nuclear Overhauser effect (13% intensity enhancement) was observed on irradiation at the C-7 methylene. It is therefore formulated as the (*E*)-12,13-didehydro-compound (16) rather than as (15). The same characteristic resonances were also observed for a solution of the crude reaction mixture in deuteriochloroform and therefore the isomerisation of the initially formed 13,14-didehydro-compound (15) to (16) was not a consequence of the isolation procedure. Moreover, when the Wittig reaction was carried out in dimethyl sulphoxide at room temperature for 2 days, the product was again (16). Sodium borohydride reduction of (16) gave a somewhat unstable hydroxyoctylidene compound



(19) (20) (21) (22)

SCHEME 2

(17). Catalytic hydrogenation of (16) over palladium–charcoal yielded the saturated ketone (18) which on reduction with borohydride afforded the stable hydroxyoctyl compound (3b) as a separable (h.p.l.c.) mixture of diastereoisomers.

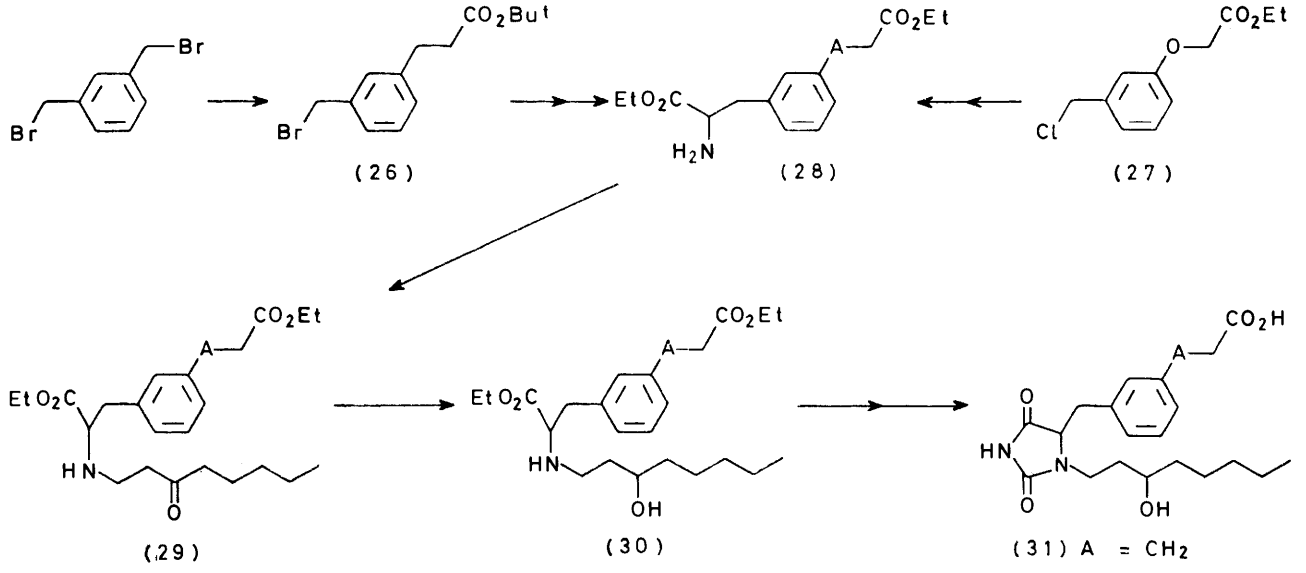


(24) (25)

SCHEME 3

The less polar diastereoisomer of (3b) had 1/40th of the potency of prostaglandin E_1 (PGE_1) as an inhibitor of platelet aggregation in human platelet-rich plasma, whilst the more polar isomer was markedly less active. In contrast, the less polar diastereoisomer of (2b), again the more active of the two isomers, was of considerable interest since it was about twice as potent as PGE_1 in this test system. A number of analogues (22) (Scheme 2 and Table 1) were next prepared to investigate the

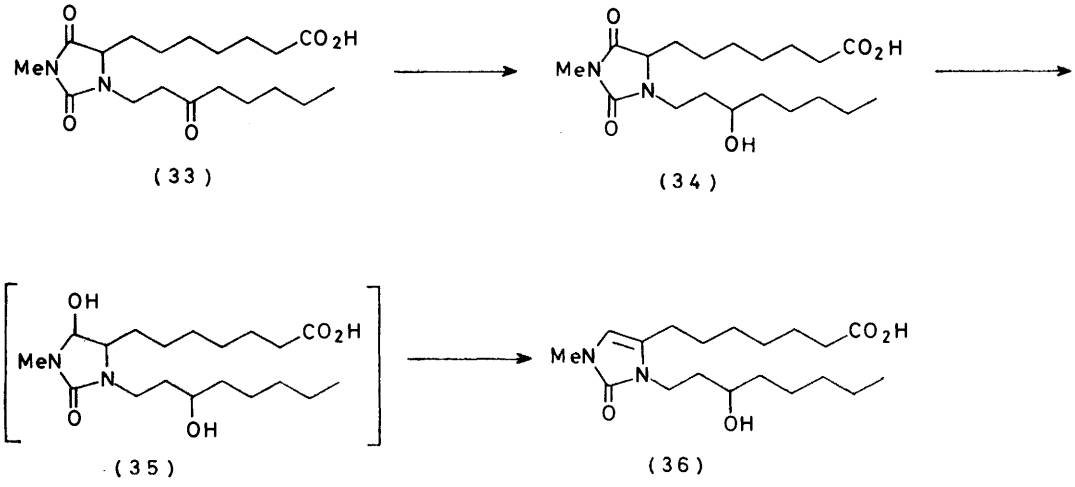
effect of replacement of the terminal C_5H_{11} of (2b) by other groups. The ketones (20) were obtained by Michael-type addition [8] of diethyl 2-aminononanedioate [9] to vinyl ketones; reduction with sodium borohydride afforded the secondary alcohols (21) which were con-



SCHEME 4

verted by the method described above into the hydantoins (22), each of which afforded (h.p.l.c.) two diastereoisomers. It was found in all cases that the less polar isomer had the greater biological potency. The diastereoisomers were also distinguishable by ^1H n.m.r. spectroscopy, the C-13 protons in the less polar isomers exhibiting a greater degree of non-equivalence (chemical shift separation 0.5—0.9 p.p.m.) than those in the more polar isomers (separation 0.0—0.2 p.p.m.). The less polar diastereoisomer of (22; R = cyclohexyl) has striking biological activity, having about 14 times the anti-aggregatory potency of PGE_1,* and it also has selectivity of action, causing less vasodilatation than PGE_1. The less active diastereoisomer of (22; R = cyclohexyl), like all members of the series, can be epimerised by base to provide more of the highly active diastereoisomer.

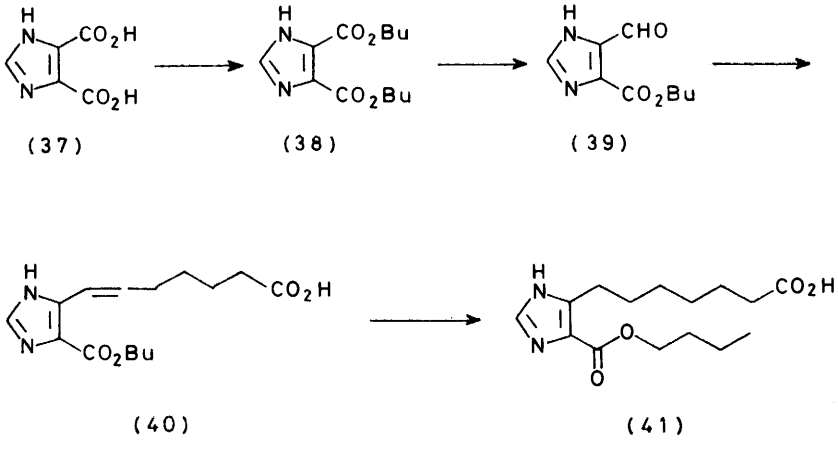
Since the 15-methyl derivatives of the E and F prostaglandins have a different profile and longer duration of biological actions than the parent compounds, it was desirable to examine the 15-methyl derivative (25) of the prototype (2b). This derivative was synthesised from diethyl 2-aminononanedioate (19) as shown in Scheme 3. The less polar diastereoisomer of (25) was considerably less potent than that of (2b) as an anti-aggregatory agent and it also had the disadvantage of causing diarrhoea in small animals.



SCHEME 5

* Other very potent analogues will be the subject of a later communication.

It has been reported [10] that introduction of the *m*-phenylene and *m*-oxaphenylene moieties into the acid side-chain of prostaglandin E_1 markedly increases the anti-aggregatory potency. The hydantoin derivative (31) was therefore synthesised (Scheme 4), the required intermediate (26) being prepared from 1,3-bisbromomethylbenzene by reaction with one equivalent of lithio-t-butyl acetate in the presence of hexamethylphosphoramide.[11] Reaction at the second bromomethyl group, to give a diester, was not detected under these conditions. Similarly, the hydantoin analogue (32) was synthesised (Scheme 4) from the known [12] intermediate (27). In the event, the less polar diastereoisomer of the hydantoin (31) had only weak anti-aggregatory properties. The



SCHEME 6

diastereoisomers of hydantoin (32) were not separable, attributable perhaps to the considerably higher polarity of this species, but the mixture had only moderate anti-aggregatory activity.

In the early stages of these studies, the *N*-methylhydantoin (33) was obtained (Scheme 5) by reaction of the intermediate (4c) with methyl isocyanate followed by alkaline hydrolysis. When this was reduced with 2 equiv. of borohydride, only the expected 15-hydroxy-compound (34) was formed, but in the presence of a considerable excess of borohydride the imidazolone (36) was the principal product, arising presumably *via* the intermediacy of (35). It was not possible to over-reduce the parent compound (2b). Compounds (34) and (36) were weak inhibitors of platelet aggregation.

Synthesis of another imidazole prostaglandin analogue (41) was also investigated (Scheme 6). The readily prepared dicarboxylic acid (37) was first converted into the dibutyl ester (38) and then reduced with sodium dihydrobis(methoxyethoxy)aluminate (RED-AL) in tetrahydrofuran at −20 °C, providing the mono-aldehyde (39) in 55% yield. Reaction of (39) with the anion of (5-carboxypentylidene)triphenylphosphorane in dimethyl sulphoxide gave a mixture of *E*- and *Z*-isomers (40) which, on catalytic hydrogenation, afforded the 6-carboxyhexyl compound (41). The latter had some interesting biological properties, being an inhibitor of platelet aggregation and also antagonising the spasmogenic effect of PGE_1 on the guinea pig ileum.

EXPERIMENTAL

Thin layer chromatograms (t.l.c.) were performed on Merck silica gel 60 F_{254} or Merck alumina 60 (Type E) plates, and were developed in iodine vapour. Hopkin and Williams silica gel (60—120 mesh) was used for gravity column chromatography and Bio-sil silica (20—44 μ) for high performance liquid chromatography. ^1H N.m.r. spectra were determined for solutions in deuteriochloroform unless otherwise stated, using a Bruker HFX-90 or a Varian HA-100 spectrometer; characteristic signals only are quoted. E.i. mass spectra were obtained on an A.E.I. MS902 spectrometer at 70 eV and c.i. mass spectra on a VG 7070F spectrometer using either ammonia or isobutane as reagent gas; both mass spectrometers were interfaced to a VG MULTISPEC data system.

5-(6-*Carboxyhexyl*)-1-*octylhydantoin* (2a).—To a solution of diethyl 2-octylaminononanedioate (4a) [1,2a] (14 g) in ethanol (75 ml) and 2N-hydrochloric acid (37.7 ml) was slowly added a solution of potassium cyanate (6.11 g) in water (18 ml) with stirring and cooling in ice–water. The resulting solution, which soon became turbid, was allowed to stand at room temperature for 17 h. The ethanol was evaporated off, water added, and the insoluble oil extracted into ether. The ether was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated to leave an oil (14.5 g) consisting of components having R_F 0.25 and 0.45 (SiO_2; $CHCl_3$–MeOH, 50 : 1). A solution of this oil in light petroleum (b.p. 60—80°) (15 ml) was heated under reflux for 3½ h, during which time the slower running component gradually disappeared and the other increased. The solvent was evaporated off and the residual oil (13.8 g) was dissolved in light petroleum (b.p. 40—60°) (70 ml) and filtered from a small amount of insoluble white solid, m.p. 188—189°, identified as ethyl allophanate; the filtrate was cooled to give needles (11.8 g), m.p. 46—48°, of the *ester* (6a) (Found: C, 65.55; H, 9.95; N, 7.65. $C_{20}H_{36}N_2O_4$ requires C, 65.2; H, 9.85; N, 7.6%), δ 2.93 and 3.69 (each 1 H, m, non-equiv. NCH_2), 4.01 (1 H, t, >CH–), 4.12 (2 H, q, CO_2CH_2Me), and 9.3br (1 H, s, NH).

A solution of the ester (6a) (5 g) in 1N-aqueous sodium hydroxide (34 ml) was left at room temperature for 2¼ h, then washed with ether and acidified with hydrochloric

acid. The precipitated oil was extracted into ether, the extract was washed with water, dried ($MgSO_4$), and concentrated to small volume, and light petroleum (b.p. 40—60°) was added to induce crystallisation of a colourless solid (4.05 g), m.p. 86—88°. Recrystallisation from methanol gave the pure *carboxylic acid* (2a) as needles, m.p. 88—89° (Found: C, 63.7; H, 9.45; N, 8.15. $C_{18}H_{32}N_2O_4$ requires C, 63.5; H, 9.45; N, 8.25%).

Ethyl 2-(6-*Ethoxycarbonylhexylamino*)*decanoate* (7a).—2-Aminodecanoic acid [13] (16 g) was added in portions to a stirred, cooled (−10 °C) mixture of ethanol (70 ml) with thionyl chloride (6 ml), and the resulting solution was set aside at room temperature for 2 h, then refluxed for 1 h, cooled, and poured into ice–water. After addition of aqueous sodium hydroxide to pH 9, the product was extracted into ether and the ethereal solution dried and evaporated; distillation gave ethyl 2-aminodecanoate (75%) as an oil,* b.p. 82—84° at 0.2 mmHg, δ 0.87 (3 H, t, 10-Me), 1.1—2.0 (17 H, $[CH_2]_7$ and OCH_2Me), 1.5br (2 H, s, NH_2), 3.40 (1 H, t, >CH−), and 4.17 (2 H, q, OCH_2Me). This ester (18 g) was heated with ethyl 7-bromoheptanoate [15] (20 g) in ethanol (50 ml) under reflux for 24 h and the ethanol was evaporated off. Addition of ether gave a hydrobromide salt, m.p. 98°, which was dissolved in dichloromethane, treated with an equivalent of triethylamine, washed repeatedly with water, and dried. Removal of the solvent and distillation yielded the *ethyl ester* (7a) (52%) as an oil, b.p. 142—144° at 0.001 mmHg, δ 2.1—2.7 (4 H, m, NCH_2 and CH_2CO_2Et), 3.16 (1 H, t, >CH−), 4.10 and 4.16 (each 2 H, q, 2 × OCH_2Me).

1-(6-*Carboxyhexyl*)-5-*octylhydantoin* (3a).—Ethyl 2-(6-ethoxycarbonylhexylamino)decanoate (7a) (7.42 g) in ethanol (40 ml) and 2N-hydrochloric acid (20 ml) was treated with a solution of potassium cyanate (3.24 g) in water (10 ml) as described above, and worked up after 72 h at room temperature to give an oil (7.7 g), R_F 0.5 (main component) and 0.65 (SiO_2; $CHCl_3$–MeOH, 19 : 1), $\nu_{max.}$ (film) 1 605 and 1 665 (urea), and 1 740 cm^{-1} (ester). The oil was heated on a steam-bath for 3 h, and the product was crystallised from light petroleum (b.p. 60—80°) to give the *hydantoin ester* (5.95 g), m.p. 68—70° (Found: C, 65.0; H, 9.9; N, 7.3. $C_{20}H_{36}N_2O_4$ requires C, 65.2; H, 9.85; N, 7.6%), $\nu_{max.}$ 1 710 and 1 770 (hydantoin), and 1 740 cm^{-1} (ester), δ 0.88 (3 H, t, octyl Me), 2.96 and 3.68 (each 1 H, m, non-equiv. NCH_2), 4.01 (1 H, t, >CH−), 4.13 (2 H, q, CO_2CH_2Me), and 8.9br (1 H, s, NH).

Hydrolysis of this ester (4 g) with aqueous sodium hydroxide gave the *carboxylic acid* (3a) (2.8 g) which crystallised from ethyl acetate–light petroleum (b.p. 60—80°) as flat needles, m.p. 65—66° (Found: C, 63.5; H, 9.85; N, 8.0. $C_{18}H_{32}N_2O_4$ requires C, 63.5; H, 9.45; N, 8.25%).

Preparation of Vinyl Ketones.—The appropriate carboxylic acid chloride was treated with ethylene in the presence of aluminium chloride under conditions similar to those recently published,[16] to give the corresponding 2-chloroethyl ketone.

The chloro-ketone was stirred vigorously on a steam-bath with freshly-ignited sodium carbonate (*cf.* ref. 17) under nitrogen for 1 h. The mixture was cooled, ether was added, and the solid was removed by filtration and washed well with ether. The ethereal filtrate was dried ($MgSO_4$) and evaporated, and the product was distilled under reduced pressure to give the pure vinyl ketone (50—70%). Prepared by this method were oct-1-en-3-one,[16] b.p. 61—62° at 12 mmHg (lit.,[16] 63—65° at 14 mmHg), n_D^{22} 1.433 8; dec-1-en-3-one,[16] b.p. 81—83° at 7 mmHg (lit.,[16] 96° at 16 mmHg); 1-*cyclobutylprop*-2-*en*-1-*one*, b.p. 61—61.5° at 26 mmHg; 1-cyclopentylprop-2-en-1-one,[18] b.p. 69° at 18 mmHg, $n_D^{16.5}$ 1.470 0; 1-cyclohexylprop-2-en-1-one,[19] b.p. 83—85° at 14 mmHg (lit.,[19] 93—94° at 12 mmHg), n_D^{24} 1.471 0; and 1-*cycloheptylprop*-2-*en*-1-*one*, b.p. 119—121° at 20 mmHg, n_D^{24} 1.483 0. 2,2-Dimethylpent-4-en-3-one,[20] b.p. 70—70.5° at 132 mmHg (lit.,[20] 65—66° at 105 mmHg), n_D^{28} 1.418 0, was prepared from the Mannich base derived from pinacoline following the general procedure of Beke and Szántay.[21]

5-(6-*Carboxyhexyl*)-1-(3-*hydroxyoctyl*)*hydantoin* (2b).—Diethyl 2-aminononanedioate [9] (10.4 g) and oct-1-en-3-one (5.04 g) were mixed at 0 °C and set aside at room temperature overnight, giving *diethyl* 2-(3-*oxo-octylamino*)*nonanedioate* (4c) as an oil, δ 2.3 (4 H, m, $-CH_2\cdot CO_2Et$ and >N·CH_2·CH_2·CO−), 3.16 (1 H, t, >CH−), and 4.11 and 4.17 (each 2 H, q, CO_2CH_2Me). A stirred solution of this ketone (13.5 g) in ethanol (140 ml) was treated dropwise at 0 °C with sodium borohydride (665 mg) in ethanol (70 ml), kept at room temperature for 3½ h, and then concentrated at 40 °C *in vacuo*. Water was added, the mixture was brought to pH 6 by addition of dilute hydrochloric acid, and the product was extracted into ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to give diethyl 2-(3-hydroxyoctylamino)nonanedioate (4b) as an oil consisting of two diastereoisomers, R_F 0.40 and 0.45 (SiO_2; $CHCl_3$–MeOH, 50 : 1) and minor impurities which could be removed by chromatography (SiO_2; $CHCl_3$–MeOH, 50 : 1). To the foregoing crude amino-alcohol (4 g), dissolved in ethanol (20 ml) and 2N-hydrochloric acid (10 ml), a solution of potassium cyanate (1.62 g) in water (5 ml) was added gradually with cooling and stirring, and the solution was left at room temperature overnight. Most of the alcohol was evaporated, water was added, and the oil was extracted into ether. Evaporation of the washed and dried ethereal solution left an oil which was heated on the steam-bath for 5 h, to give the crude ester (6b) as a yellow oily mixture (4.1 g) of diastereoisomers, R_F 0.55 and 0.65 (SiO_2; $CHCl_3$–MeOH, 9 : 1), containing some impurities. The crude ester (4.1 g) was stirred with 0.5N-aqueous sodium hydroxide (50 ml) for 2½ h. The insoluble non-acidic material was removed by washing with ether and the clear alkaline solution was acidified with 2N-hydrochloric acid; the liberated carboxylic acid was extracted into ether and the ethereal solution was washed with water, dried, and evaporated to give the *carboxylic acid* (2b) as a pale yellow viscous oil (3.25 g) showing the two diastereoisomers, R_F 0.60 and 0.65, with only trace impurities, on t.l.c. (SiO_2; $CHCl_3$–MeOH–HOAc, 90 : 5 : 5). Column chromatography (SiO_2; $CHCl_3$–MeOH) afforded a pure sample (Found: C, 60.55; H, 9.0; N, 8.1. $C_{18}H_{32}N_2O_5$ requires C, 60.65; H, 9.05; N, 7.85%). The individual diastereoisomers were obtained by high performance liquid chromatography (h.p.l.c.) (SiO_2; $CHCl_3$–MeOH–HOAc, 98.25 : 1.25 : 0.5); both solidified and were recrystallised from ethyl acetate–light petroleum (b.p. 60—80°) (see Table). The less polar compound gave δ 0.86 (3 H, t, Me), 2.31 (2 H, t, CH_2CO_2H), 3.05 and 3.83 (each 1 H, m, non-equiv. NCH_2), 3.51 (1 H, m, >CH·OH), 4.03 (1 H, t, N−CH<) and *ca.* 9.1vbr (1 H, NH), whereas the more polar compound gave δ 0.86 (3 H, t, Me), 2.29 (2 H, t, CH_2CO_2H), 3.6 (3 H, m, NCH_2 and >CHOH), and 4.07 (1 H, t, N−CH<).

* Stork *et al.*[14] give m.p. 69—71° for this compound, perhaps as the hydrochloride.

The above general method was used for the preparation of the hydantoin derivatives listed in Table 1.

5-(6-Carboxyhexyl)-1-(3-oxo-octyl)hydantoin and its Reduction.—Treatment of diethyl 2-(3-oxo-octylamino)-nonanedioate (4c) with potassium cyanate and hydrochloric acid, and subsequent heating of the derived product, as described above, yielded the crude hydantoin ester (6c) (t.l.c. indicated much impurity). This crude ester (800 mg) was stirred with 1N-aqueous sodium hydroxide (6 ml) at room temperature for 1.5 h and worked up in the normal way to give non-acidic (300 mg) and acidic (300 mg) products as yellow oils. The acidic material was freed from minor impurities by chromatography (SiO_2; $CHCl_3$–MeOH, 50 : 1) to give 5-(6-*carboxyhexyl*)-1-(3-*oxo-octyl*)-*hydantoin* as a pale yellow viscous oil, solidifying on long standing, m.p. 55—58° (Found: C, 60.8; H, 8.5; N, 7.6. $C_{18}H_{30}N_2O_5$ requires C, 61.0; H, 8.55; N, 7.9%), δ 2.34 (2 H, t, CH_2CO_2H), 3.32 and 3.78 (each 1 H, m, non-equiv. NCH_2), 4.08 (1 H, t, >CH–), and 9.34br (1 H, s, NH). A solution of this keto-acid (1.6 g) in 1N-aqueous sodium hydroxide (9.2 ml) was stirred and cooled in ice during the gradual addition of sodium borohydride (350 mg), then stirred at room temperature for 4 h. Water was added, the solution was washed with ether, and the aqueous phase was acidified and extracted with ether. The washed and dried extract was evaporated to give 5-(6-carboxyhexyl)-1-(3-hydroxyoctyl)hydantoin (2b) (1.37 g), identical (t.l.c., ^1H n.m.r. spectrum) with the compound described above.

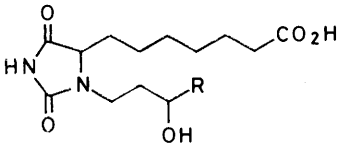
Separation of the Diastereoisomers of Diethyl 2-(3-Hydroxyoctylamino)nonanedioate (4b).—A solution of the mixture of diastereoisomers (4b) (200 mg) in ether (2 ml) was treated with a slight excess of ethereal hydrogen chloride and the solution was rubbed and cooled to induce crystallisation. After 4 h at 0 °C, the solid was collected and recrystallised from ethyl acetate–light petroleum (b.p. 60—80°) to give small plates, m.p. [of the *hydrochloride* of one diastereoisomer of (4b)] 95—96.5° (Found: C, 59.45; H, 9.95; Cl, 8.6; N, 3.1. $C_{21}H_{42}ClNO_5$ requires C, 59.5; H, 10.0; Cl, 8.35; N, 3.3%). The derived (aq. KOH–Et_2O) *base* was an oil, R_F 0.45 (SiO_2; $CHCl_3$–MeOH, 50 : 1), δ 2.43 and 2.99 (each 1 H, m, non-equiv. NCH_2), 3.11 (1 H, m, N–CH<), 3.69 (1 H, m, –CHOH), and 4.08 (4 H, q, 2 × CO_2CH_2Me). Evaporation of the original ether filtrate left the oily *hydrochloride* of predominantly the second diastereoisomer of (4b) which gave an oily *base*, R_F 0.40 (SiO_2; $CHCl_3$–MeOH, 50 : 1), δ 2.76 (2 H, m, NCH_2), 3.72 (1 H, m, >CH–OH), and 4.13 (4 H, q, 2 × CO_2CH_2Me).

Preparation of Individual Diastereoisomers of 5-(6-Carboxyhexyl)-1-(3-hydroxyoctyl)hydantoin (2b).—By treatment with potassium cyanate and hydrochloric acid as described above, the less polar diastereoisomer of the intermediate (4b) was converted into the more polar diastereoisomer of the hydantoin ethyl ester (6b) and thence, by exposure to 2.2 equiv. 0.5N-aqueous sodium hydroxide at room temperature for 1 h, into the more polar diastereoisomer, m.p. 63—65°, of the hydantoin-carboxylic acid (2b).

Similarly, the more polar diastereoisomer of (4b) gave the less polar diastereoisomer, m.p. 76—78°, of the hydantoin-carboxylic acid (2b).

Diethyl Acetamido-(3-hydroxyoctyl)malonate (8). Diethyl acetamidomalonate (16.4 g) and triethylamine (11.3 g) were dissolved in ice-cold ethanol (80 ml) and oct-1-en-3-one (19.1 g) was added dropwise. After the initial mildly exothermic reaction had subsided, the solution was set aside at room temperature for 3 h. The solvent was removed *in vacuo* and the residual crystalline mass was triturated with cold light petroleum (b.p. 60—80°), collected, and recrystallised from ether–hexane, giving *diethyl acetamido-(3-oxo-octyl)malonate* as white feathery needles (24.0 g), m.p. 65—66° (Found: C, 59.45; H, 9.0; N, 4.15. $C_{17}H_{29}NO_6$ requires C, 59.5; H, 8.45; N, 4.1%), δ 0.87 (3 H, t, octyl Me), 2.03 (3 H, s, COMe), 4.22 (4 H, q, 2 × CO_2CH_2Me), and 6.7br (1 H, s, NH). This ketone (1.7 g, 5 mmol) was stirred in ethanol (20 ml) at −25 °C and treated dropwise over 15 min with a solution of sodium borohydride (100 mg, 2.5 mmol) in ethanol (15 ml). The

Hydantoin derivatives



R	Diastereo-isomer	M.p. (°)	Mol. formula	Found (%) C	H	N	Required (%) C	H	N	Inhibition of platelet aggregation × PGE_1
Pentyl	Less polar	76—78	$C_{18}H_{32}N_2O_5$	60.35	8.95	7.75	60.65	9.05	7.85	2
	More polar	63—65		60.75	8.95	7.7				0.05
Heptyl	Less polar	68—70	$C_{20}H_{36}N_2O_5$	62.3	9.55	7.45	62.45	9.45	7.3	0.05
	More polar	82—83		62.45	9.4	7.15				0.01
t-Butyl	Less polar	114—115	$C_{17}H_{30}N_2O_5$	59.7	9.15	8.05	59.65	8.85	8.2	0.15
		93—95 *		59.9	9.0	8.0				
	More polar	144—146		59.95	8.85	8.45				0.05
Cyclobutyl	Less polar	114—116	$C_{17}H_{28}N_2O_5$	59.85	8.4	8.1	60.0	8.3	8.25	5
	More polar	103—105		60.1	8.5	8.05				0.6
Cyclopentyl	Less polar	116—117	$C_{18}H_{30}N_2O_5$	60.3	8.8	7.55	61.0	8.55	7.9	8
		92—94 *								
	More polar	97—99		60.65	8.2	7.7				1
Cyclohexyl	Less polar	96—98	$C_{19}H_{32}N_2O_5$	62.3	8.65	7.45	61.95	8.75	7.6	14
		129—131 *		61.95	8.8	7.5				
	More polar	124—126		62.05	8.7	7.4				0.2
Cycloheptyl	Less polar	107—109	$C_{20}H_{34}N_2O_5$	62.65	8.85	7.25	62.8	8.75	7.3	1
	More polar	107—109		63.2	8.95	7.1				0.1

* Different crystalline form.

mixture was then stirred at 0 °C for 18 h, acidified to pH *ca.* 6 with 2N-hydrochloric acid, diluted with water, and the resulting clear solution was shaken with chloroform. The chloroform solution was dried and concentrated *in vacuo* and the residual colourless syrup was purified by column chromatography (Laporte, Grade I, Al_2O_3; $CHCl_3$–EtOH, 19 : 1) affording *diethyl acetamido-(3-hydroxyoctyl)-malonate* (8) as a gum (1.06 g), δ 0.88 (3 H, t, octyl Me), 1.7br (1 H, s, OH), 2.02 (3 H, s, COMe), 3.54 (1 H, m, >C*H*OH), 4.22 (4 H, q, 2 × CO_2CH_2Me), and 6.8br (1 H, s, NH).

1-(6-*Carboxyhexyl*)*hydantoin*-5-*carbaldehyde* (14).—A stirred suspension of sodium hydride (25.2 g) in dry ether (500 ml) was treated with ethanol (1 ml) and then dropwise during 3½ h with a mixture of *N*-formylglycine ethyl ester [6] (125 g) and ethyl formate (196 g), keeping the temperature at 10—15 °C throughout. The resulting suspension of fine solid was stirred at 12 °C overnight, the ether was evaporated in a current of nitrogen, and the residual sodium derivative of *N*,2-diformylglycine ethyl ester (10) was treated with butanolic hydrogen chloride as described in ref. 7, affording 2-(dibutoxymethyl)glycine ethyl ester (11) (85.9 g), b.p. 80—83° at 0.06 mmHg (lit.,[7] 98° at 0.04 mmHg) (Found: C, 59.8; H, 10.45; N, 5.35. Calc. for $C_{13}H_{27}NO_4$: C, 59.75; H, 10.4; N, 5.35%). Compound (11) (30 g) was heated with ethyl 7-bromoheptanoate (27.24 g, 1 mol equiv.) under nitrogen in an oil-bath at 100 °C for 3 h, to give crude ethyl 7-[(2,2-dibutoxy-1-ethoxycarbonylethyl)amino]heptanoate (12) hydrobromide, R_F (free base) 0.37 (SiO_2; $CHCl_3$). Reaction of this product (57.2 g) with cyanic acid and work-up according to the general procedure described for hydantoin (2b) yielded crude 5-dibutoxymethyl-1-(6-ethoxycarbonylhexyl)hydantoin (51.6 g) as an oil. A pure sample, obtained by column chromatography (SiO_2; Et_2O) had R_F 0.14 (SiO_2; $CHCl_3$) and gave characteristic signals, δ 2.30 (2 H, t, CH_2CO_2Et), 3.6 (6 H, m, NCH_2 and $CH_2OCHOCH_2$), 4.08 and 4.79 (each 1 H, both d, *J* 1.5 Hz, mutual coupling confirmed by spin decoupling, >CH–CH<), and 8.4br (1 H, s, NH). The crude hydantoin (48.9 g) was stirred in ether (196 ml) with 0.33N-aqueous sodium hydroxide (1 220 ml) for 1.5 h at room temperature and the mixture was shaken with ether (900 ml); the aqueous phase was separated, brought to pH *ca.* 8 with carbon dioxide and washed with ether (2 × 350 ml), and the washings were re-extracted * with 0.33N-aqueous sodium hydrogencarbonate (2 × 900 ml). The aqueous solutions were combined, cooled in ice–water and acidified with hydrochloric acid; the liberated carboxylic acid was taken into ether, the ethereal solution washed with water and dried ($MgSO_4$), and the ether evaporated. The residual oil was purified by column chromatography (SiO_2; Et_2O) to give pure 1-(6-*carboxyhexyl*)-5-*dibutoxymethylhydantoin* (13) (26.8 g) as an oil, δ 2.34 (2 H, t, CH_2CO_2H), 3.6 (6 H, m, NCH_2 and $CH_2OCHOCH_2$), 4.09 and 4.80 (each 1 H, both d, *J* 1.5 Hz, >CH–CH<), 9.0br (1 H, s, NH), and 10.8br (1 H, CO_2H).

A solution of hydantoin (13) (25.8 g) in ice-cold concentrated hydrochloric acid (103 ml) was set aside at room temperature for 2 h. The resulting suspension of crystals was cooled in ice–water, diluted with water (130 ml), set aside for 15 min, and filtered; the crystals were washed with water, dried *in vacuo*, suspended in ether (70 ml) and collected, affording, 1-(6-*carboxyhexyl*)*hydantoin*-5-*carbaldehyde* (14) (15.0 g), m.p. 223—225°, R_F 0.70 (SiO_2; BuOH–HOAc–H_2O, 100 : 1 : 1) (Found: C, 51.3; H, 6.45; N, 10.85. $C_{11}H_{16}N_2O_5$ requires C, 51.55; H, 6.3; N, 10.95%), δ([$^2H_6$]DMSO) 2.18 (2 H, t, CH_2CO_2H), 3.61 (2 H, t, NCH_2), 6.88 (1 H, s, =CH–), and 10.7br (1 H, s, NH).

1-(6-*Carboxyhexyl*-5-[(E)-3-*oxo-octylidene*]*hydantoin* (16).—A mixture of the aldehyde (14) (3 g) with (2-oxoheptylidene)triphenylphosphorane [22],† (8.33 g, 1.9 mol equiv.) and benzene (4 ml) was heated under nitrogen in a bath at 100 °C for 45 min. The resulting gum [R_F 0.03 (phosphorane), 0.40 (Ph_3PO), and 0.44 (product) on SiO_2 in the A9 system [23]] was subjected to column chromatography on silica (200 g), elution with the A9 system yielding the pure *hydantoin* (16) (3.06 g), a pale yellow gum which slowly crystallised on standing, δ 0.89 (3 H, t, Me), 3.58 (2 H, t, NCH_2), 3.93 (2 H, d, =CH–CH_2–CO) coupled, *J* 7.1 Hz, to 5.72 (1 H, t, =CH–), and 8.4br (1 H, s, NH). A mixture (2 g) consisting of *ca.* equal parts of hydantoin (16) and triphenylphosphine oxide was obtained from later chromatographic fractions.

1-(6-*Carboxyhexyl*)-5-[(E)-3-*hydroxyoctylidene*]*hydantoin* (17).—Treatment of the oxo-octylidene compound (16) in aqueous sodium hydrogencarbonate with sodium borohydride and purification of the reduction product by column chromatography (SiO_2; H_2O–saturated EtOAc) afforded the *hydantoin* (17) as a pale yellow oil, R_F 0.36 (SiO_2; H_2O–saturated EtOAc), δ 3.54 (2 H, t, NCH_2), 3.77 (1 H, m, >C*H*OH), 2.90 (2 H, m, =CH–CH_2–CHOH), 5.61 (1 H, t, =CH–), and 9.1br (1 H, s, NH).

1-(6-*Carboxyhexyl*)-5-(3-*oxo-octyl*)*hydantoin* (18).—A solution of the oxo-octylidene compound (16) (3.06 g) in ethanol (60 ml) was stirred with 10% palladium–charcoal (200 mg) under hydrogen [uptake 193 ml (23 °C and 752 mmHg) during 130 min]. The filtered solution was evaporated and the residual oil treated with ether (4 ml) to give crystals (2.58 g), m.p. 84.5—86°, of the *hydantoin* (18) (Found: C, 60.85; H, 8.55; N, 7.85. $C_{18}H_{30}N_2O_5$ requires C, 61.0; H, 8.55; N, 7.9%), δ 3.04 and 3.60 (each 1 H, m, non-equiv. NCH_2), 4.01 (1 H, dd, –CH–), and 9.1br (1 H, s, NH).

1-(6-*Carboxyhexyl*)-5-(3-*hydroxyoctyl*)*hydantoin* (3b).—A stirred, ice-cooled suspension of the oxo-octyl compound (18) (0.5 g) in water (15 ml) was treated with sodium hydrogencarbonate (0.36 g) and, during 3 min, with sodium borohydride (54 mg). After 45 min, more sodium borohydride (54 mg) was added and, after a further 75 min, the clear solution was set aside for 1.5 h and then acidified with hydrochloric acid. The liberated carboxylic acid was taken into chloroform (2 × 30 ml) and the chloroform solution was washed with water, dried ($MgSO_4$), and evaporated. The residual mixture of diastereoisomers [R_F 0.44 and 0.40 (SiO_2; $CHCl_3$–MeOH–HOAc, 90 : 5 : 5)] was subjected to high performance liquid chromatography (SiO_2; $CHCl_3$–MeOH–HOAc, 97.75 : 1.25 : 1) to give the *less polar hydantoin* (3b) as a gum (200 mg) (Found: M^+, 356.228 0. $C_{18}H_{32}N_2O_5$ requires *M*, 356.231 1), δ 3.09 (1 H, m, one NCH_2 proton), 3.58 (2 H, m, one NCH_2 proton and >C*H*OH), 4.09 (1 H, t, N–CH<), and 9.0br (1 H, s, NH), and the *more polar hydantoin* (3b) as a gum (207 mg) (Found: M^+, 356.227 7), δ 3.07 (1 H, m, one NCH_2 proton), 3.59 (2 H, m,

* The exhausted ethereal washings were dried ($MgSO_4$) and evaporated to give *5-dibutoxymethylhydantoin* as a gum (4.8 g), R_F 0.34 (silica; ether), δ 3.6 (4 H, m, $CH_2OCHOCH_2$), 4.20 and 4.74 (each 1 H, both d, *J* 2.9 Hz, >CH–CH<), 6.1br (1 H, s, 1-NH), and 8.9br (1 H, s, 3-NH).

† In our hands this phosphorane crystallised: it was suspended in light petrolem and collected, m.p. 76.5—77.5°.

one NCH_2 proton and >CHOH), 4.08 (1 H, t, N–CH<), and 9.1br (1 H, s, NH). The latter solidified on long standing.

5-(6-*Carboxyhexyl*)-1-(3-*hydroxy*-3-*methyloctyl*)*hydantoin* (25).—Oct-1-en-3-one (63 g) stirred in dry ether (100 ml) at 0 °C was treated dropwise with a freshly-prepared solution of hydrogen bromide (40 g) in dry ether (200 ml). The resulting solution was stirred at room temperature for 0.5 h, then added slowly to a solution of methylmagnesium iodide [from methyl iodide (85 g), magnesium turnings (15 g), and dry ether (350 ml)] so as to maintain a steady reflux. The mixture was stirred at room temperature for 2 h, treated with saturated aqueous ammonium chloride, and filtered (Celite), and the filtrate was dried and concentrated *in vacuo*. The residual yellow oil was percolated through a silica column in 40% v/v ether–light petroleum (b.p. 60—80°) and finally purified by distillation, giving 1-*bromo*-3-*hydroxy*-3-*methyloctane* (23) as a pale yellow oil (52.5 g), b.p. 71—74° at 0.03—0.04 mmHg, δ 0.90 (3 H, t, terminal Me), 1.20 (3 H, s, 3-Me), 1.43 (1 H, s, OH), 2.05 (2 H, m, 2-CH_2), and 3.50 (2 H, m, 1-CH_2).

The bromo-compound (23) (4.5 g) was heated with diethyl 2-aminononanedioate (5.2 g) in ethanol (20 ml) under reflux for 20 h, the solvent was evaporated off, water was added, and the mixture was basified and extracted with ether. The ethereal solution was washed, dried, and evaporated to leave a yellow oil (7.4 g) which was subjected to chromatography (SiO_2; H_2O-saturated EtOAc) to give almost pure diethyl 2-(3-hydroxy-3-methyloctylamino)nonanedioate (24) (4.3 g), R_F 0.5 (SiO_2; Et_2O). Treatment of the foregoing amino-diester (4.3 g) with potassium cyanate and hydrochloric acid as described above, followed by heating of the product, gave crude 5-(6-ethoxycarbonylhexyl)-1-(3-hydroxy-3-methyloctyl)hydantoin (4.5 g). Hydrolysis of the crude ester with 0.5N-aqueous sodium hydroxide and work-up in the normal manner yielded the *hydantoin-carboxylic acid* (25) (2.8 g) as a pale yellow oil which gave only one spot, R_F 0.6, on t.l.c. (SiO_2; $CHCl_3$–MeOH–HOAc, 90 : 5 : 5) (Found: C, 61.05; H, 9.4; N, 7.35. $C_{19}H_{34}N_2O_5$ requires C, 61.6; H, 9.25; N, 7.55%). Only a partial separation of the diastereoisomers was achieved by h.p.l.c., even after recycling several times, but the less polar fraction solidified and gave small prisms, m.p. 105—107° (from EtOAc) of the pure less polar *diastereoisomer* (Found: C, 61.35; H, 9.0; N, 7.25%), δ 1.21 (3 H, s, Me), 2.32 (2 H, t, CH_2CO_2H), 3.11 and 3.79 (each 1 H, m, non-equiv. NCH_2), 4.07 (1 H, t, >CH–), and 9.14br (1 H, s, NH).

t-Butyl 3-(3-*Bromomethylphenyl*)*propionate* (26).—A solution of di-isopropylamine (4.04 g) and butyl-lithium (25 ml; 1.60M-solution in hexane) in dry tetrahydrofuran (40 ml), stirred at −78 °C under dry nitrogen, was treated during 5 min with t-butyl acetate (4.64 g) and then, during a further 5 min, with a solution of 1,3-bisbromomethylbenzene (11.6 g) and dry hexamethylphosphoramide (1.42 g) in dry tetahydrofuran (8 ml). The resulting yellow solution was stirred at −78 °C for 0.5 h, brought to room temperature over 3 h, treated with ice–water, and extracted with ether. The extract was washed with 1N-hydrochloric acid (60 ml), then with water, dried, evaporated, and the residual yellow oil was purified by column chromatography (SiO_2; Et_2O–hexane, 1 : 1), to give the *bromomethyl* compound (26) as an oil (6.6 g), δ 1.42 (9 H, s, CMe_3), 2.3—3.1 (4 H, m, CH_2CH_2), 4.47 (2 H, s, $BrCH_2$), and 7.22br (4 H, ArH). 1,3-Bisbromomethylbenzene (4.1 g) was recovered from the column fractions.

Ethyl 2-*Amino*-3-[3-(2-*ethoxycarbonylethyl*)*phenyl*]-*propionate* (28; A = CH_2).—A solution of sodium (1.87 g) in dry ethanol (82 ml) was treated with diethyl acetamidomalonate (19.5 g) followed by the bromomethyl compound (26) (24.3 g) and heated under reflux for 18 h. The cooled suspension was diluted with water, the product extracted into ether, and the ethereal solution dried (Na_2SO_4) and evaporated. A suspension of the residual crude diethyl 2-acetamido-2-[3-(2-t-butoxycarbonylethyl)benzyl]malonate in 10% hydrochloric acid (600 ml) was heated under reflux for 5½ h and the resulting solution evaporated *in vacuo*, final traces of water being removed by azeotropic distillation with ethanol. The residual semi-solid amino-diacid was esterified using thionyl chloride (16 ml) and ethanol (240 ml), in the manner described for 2-aminodecanoic acid [see preparation of the intermediate (7a)], and the product was purified by chromatography (SiO_2; Et_2O–EtOH, 50 : 1), yielding the *amino-diester* (28; A = CH_2) as a pale yellow oil (18.9 g), δ 1.23 (6 H, t, 2 × $CO_2CH_2CH_3$), 1.5br (2 H, s, NH_2), 2.4—3.1 (6 H, m, 3-CH_2 and CH_2CH_2), 3.68 (1 H, m, >CH–), 4.12 and 4.16 (each 2 H, q, 2 × CO_2CH_2Me), and 7.1 (4 H, m, ArH).

5-[3-(2-*Carboxyethyl*)*benzyl*]-1-(3-*hydroxyoctyl*)*hydantoin* (31).—Following the general method of synthesis described above for hydantoin (2b), the amino-diester (28; A = CH_2) was converted *via* the intermediates (29; A = CH_2) and (30; A = CH_2) into the *hydantoin* (31), the diastereoisomers of which were separated by h.p.l.c. The *less polar diastereoisomer* had m.p. 82—86° (Found: C, 64.2; H, 7.9; N, 7.2. $C_{21}H_{30}N_2O_5$ requires C, 64.6; H, 7.7; N, 7.15%), *m/e* 390 (M^+) and 163 ($C_{10}H_{11}O_2^+$, base peak), δ 0.88 (3 H, t, Me), 2.58 (2 H, t, CH_2CO_2H), 2.88 (2 H, t, $ArCH_2CH_2$), 3.14 (2 H, m, >$CHCH_2Ar$), 3.48 and 3.86 (each 1 H, m, non-equiv. NCH_2), 3.65 (1 H, m, >CHOH), 4.27 (1 H, t, NCH<), 6.2br (2 H, OH and CO_2H), 7.0—7.3 (4 H, m, ArH), and 8.9br (1 H, s, NH). The *more polar diastereoisomer* had m.p. 95—97° (Found: C, 64.85; H, 7.65; N, 7.0%), *m/e* 390 (M^+), 372 ($M^+ - H_2O$), and 163 ($C_{10}H_{11}O_2^+$, base peak), δ 0.88 (3 H, t, Me), 2.59 (2 H, t, CH_2CO_2H), 2.88 (2 H, t, $ArCH_2CH_2$), 3.12 (2 H, m, >$CHCH_2Ar$), 3.52 (3 H, m, NCH_2 and >CHOH), 4.34 (1 H, t, NCH<), 6.8br (2 H, OH and CO_2H), 7.0—7.3 (4 H, m, ArH), and 9.4br (1 H, s, NH).

Diethyl 2-*Acetamido*-2-[3-(*ethoxycarbonylmethoxy*)*benzyl*]-*malonate*.—Diethyl acetamidomalonate (2.6 g) was alkylated with ethyl (3-chloromethylphenoxy)acetate [12] (27) (2.39 g) by the method described for the synthesis of compound (28; A = CH_2), giving *diethyl* 2-*acetamido*-2-[3-(*ethoxycarbonylmethoxy*)*benzyl*]*malonate* as white prisms (3.9 g), m.p. 98.5—101.5° (Found: C, 58.65; H, 7.0; N, 3.35. $C_{20}H_{27}NO_8$ requires C, 58.7; H, 6.6; N, 3.4%), δ 1.28 (9 H, t, 3 × CO_2CH_2Me), 2.03 (3 H, s, −COMe), 3.62 (2 H, s, $-CH_2Ar$), 4.26 (6 H, q, 3 × CO_2CH_2Me), 4.55 (2 H, s, $-OCH_2CO_2Et$), 6.5—6.9 (3 H, m, ArH), and 7.0—7.3 (1 H, m, ArH).

Ethyl 2-*Amino*-3-[3-(*ethoxycarbonylmethoxy*)*phenyl*]*propionate* (28; A = O).—Diethyl 2-acetamido-2-[3-(ethoxycarbonylmethoxy)benzyl]malonate (1.9 g) was hydrolysed, decarboxylated, and re-esterified in the manner described for the preparation of (28; A = CH_2), and the product was purified by chromatography (SiO_2; Et_2O–EtOH, 20 : 1) to give the *amino-diester* (28; A = O) as prisms (0.73 g), m.p. 33° (Found: C, 61.1; H, 7.05; N, 4.6. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.1; N, 4.75%), δ 1.25 and 1.29 (each 3 H, t, CO_2CH_2Me), 1.55br (2 H, s, NH_2), 2.95 (2 H, m, CH_2Ar), 3.70 (1 H, m, >CH–), 4.16 and 4.24 (each 2 H, q,

CO_2CH_2Me), 4.62 (2 H, s, OCH_2CO_2Et), 6.6—6.9 (3 H, m, 2, 4, 6-ArH), and 7.1—7.4 (1 H, m, 5-ArH).

5-[3-(*Carboxymethoxy*)*benzyl*]-1-(3-*hydroxyoctyl*)*hydantoin* (32).—The amino-diester (28; A = O) was converted [see preparations of (31) and (2b)] *via* the intermediates (29; A = O) and (30; A = O) into *hydantoin* (32) which on t.l.c. gave streaks, R_F 0.35—0.45 (SiO_2; Et_2O–HOAc, 5 : 1) and R_F 0.25—0.30 (SiO_2; $CHCl_3$–MeOH–HOAc, 90 : 5 : 5). The individual diastereoisomers were not separable by h.p.l.c. in the latter solvent system. The mixed diastereoisomers gave *m/e* (c.i.) 375 ($MH^+ - H_2O$), δ 0.88 (3 H, t, Me), 3.13 (2 H, m, >CHCH_2Ar), 3.5—4.0 (3 H, m, NCH_2 and >C*H*OH), 4.30 (1 H, m, NCH<), 4.61 (2 H, s, OCH_2CO_2H), 5.2br (2 H, OH and CO_2H), 6.6—6.9 (3 H, m, ArH), 7.1—7.3 (1 H, m, ArH), and 9.06br and 9.10br (1 H, both s, NH of two diastereoisomers). The derived *ethyl ester* gave *m/e* (e.i.) 420 (M^+), 402 ($M^+ - 18$), and 193 ($C_{11}H_{13}O_3^+$, base peak).

5-(6-*Carboxyhexyl*)-3-*methyl*-1-(3-*oxo-octyl*)*hydantoin* (33).—Diethyl 2-(3-oxo-octylamino)nonanedioate (4c) (12.8 g) in dry ether (25 ml) was added to a solution of methyl isocyanate (2.1 g) in dry ether (10 ml) and the solution left at room temperature overnight. The solvent was evaporated off and the residue was heated on a steam-bath for 2 h, to give crude 5-(6-ethoxycarbonylhexyl)-3-methyl-1-(3-oxo-octyl)hydantoin (13.2 g). Chromatography (SiO_2; $CHCl_3$–MeOH, 100 : 1) of a sample gave the pure *ester* (Found: C, 63.25; H, 9.1; N, 6.9. $C_{21}H_{36}N_2O_5$ requires C, 63.6; H, 9.15; N, 7.05%), δ 2.97 (3 H, s, NMe), 3.36 and 3.77 (each 1 H, m, non-equiv. NCH_2), 3.99 (1 H, t, >CH–), and 4.10 (2 H, q, CO_2CH_2Me). The crude ester (13 g) was stirred in ethanol (40 ml) with 5N-aqueous sodium hydroxide (10 ml) at room temperature for 3 h. Most of the alcohol was evaporated off, water was added, and the aqueous solution was washed with ether, then acidified and extracted with ether. The washed and dried extract was evaporated and the residual oil purified by chromatography (SiO_2; $CHCl_3$–MeOH, 30 : 1) to give the *carboxylic acid* (33) (8.0 g) as a pale yellow viscous oil (Found: C, 61.9; H, 9.0; N, 7.85. $C_{19}H_{32}N_2O_5$ requires C, 61.95; H, 8.75; N, 7.6%), δ 2.33 (2 H, t, CH_2CO_2H), 2.98 (3 H, s, NMe), 3.33 and 3.77 (each 1 H, m, non-equiv. NCH_2), and 3.98 (1 H, t, >CH–).

Sodium Borohydride Reduction of 5-(6-*Carboxyhexyl*)-3-*methyl*-1-(3-*oxo-octyl*)*hydantoin*.—(*a*) A stirred solution of the oxo-acid (33) (1.23 g) in 0.25N-aqueous sodium hydroxide (15 ml) was cooled in ice during the addition of sodium borohydride (62 mg, 0.5 mol. equiv.) and stirring was continued for a further 3 h at room temperature. The solution was acidified and the product was isolated by extraction with ether and purified by chromatography (SiO_2; H_2O–saturated EtOAc) to give 5-(6-*carboxyhexyl*)-1-(3-*hydroxyoctyl*)-3-*methylhydantoin* (34) almost quantitatively as an oil showing two spots (diastereoisomers), R_F 0.78 and 0.82, on t.l.c. (SiO_2; $CHCl_3$–MeOH–HOAc, 90 : 5 : 5). The individual diastereoisomers were separated by h.p.l.c., the less polar compound giving δ 2.29 (2 H, t, CH_2CO_2H), 2.98 (3 H, s, NMe), 3.09 and 3.95 (each 1 H, m, non-equiv. NCH_2), 3.49 (1 H, m, >C*H*OH), and 3.98 (1 H, t, NCH<), and the more polar compound giving δ 2.30 (2 H, t, CH_2CO_2H), 2.98 (3 H, s, NMe), 3.5 (3 H, m, NCH_2 and >C*H*OH), and 3.97 (1 H, t, NCH<).

(*b*) A stirred solution of the oxo-acid (33) (0.94 g) in 0.25N-aqueous sodium hydroxide (11.5 ml) was cooled during the addition of sodium borohydride (96 mg) and further quantities (each 96 mg) of borohydride were added after 5 and 25 h at room temperature. After an additional 24 h, the product was isolated and purified as in (*a*), to give 5-(6-*carboxyhexyl*)-1-(3-*hydroxyoctyl*)-3-*methyl*-2-*imidazolone* (36) (0.62 g) as an oil (Found: C, 64.2; H, 9.65; N, 7.75. $C_{19}H_{34}N_2O_4$ requires C, 64.4; H, 9.65; N, 7.9%), δ 2.3 (4 H, t, CH_2CO_2H and =C–CH_2), 3.2 (3 H, s, NMe), 3.5 (2 H, m, one NCH_2 proton and >C*H*OH), 3.96 (1 H, m, one NCH_2 proton), and 5.9 (1 H, t, *J* 1.3 Hz, –CH=).

Dibutyl Imidazole-4,5-*dicarboxylate* (38).*—Imidazole-4,5-dicarboxylic acid [24] (30 g) was heated with butanol (300 ml) and concentrated sulphuric acid (11 ml) under reflux for 22 h, using a Dean–Stark apparatus. Excess of butanol was evaporated *in vacuo* and a stirred suspension of the residual solid in ice–water (1 l) was basified with sodium carbonate. After the addition of chloroform (500 ml) and filtration, the chloroform phase was washed with water, dried (Na_2SO_4), and evaporated. Treatment of the residual oil with light petroleum (b.p. 40—60°; 250 ml) gave crystals (45.5 g), m.p. 107—109° (lit.,[25] 97—100°), of the dibutyl ester (38) (Found: C, 58.3; H, 7.65; N, 10.45. Calc. for $C_{13}H_{20}N_2O_4$: C, 58.2; H, 7.5; N, 10.45%), $\lambda_{max.}$ (EtOH) 251 nm (ε 8 970).

Butyl 4(5)-*Formylimidazole*-5(4)-*carboxylate* (39).—A stirred suspension of the diester (38) (20 g) in dry tetrahydrofuran (120 ml) under dry nitrogen was kept at −25 to −20 °C during the addition, over 20 min, of sodium dihydrobis-(2-methoxyethoxy)aluminate [26 ml (1.25 mol equiv.) of a 70% solution (RED-AL) in benzene]. The resulting fluid gel was then stirred at 0 °C for 45 min, cooled to −15 °C, and decomposed with water (8 ml); the gel was suspended in ethanol (1 l) and treated with a current of carbon dioxide whilst the temperature was raised to and maintained at 65 °C for 20 min. The hot solution was filtered (Hyflo), the alcohol was evaporated off and a suspension of the residual solid in water (250 ml) was saturated with carbon dioxide and filtered. The solid (13.65 g), m.p. 135—173°, a mixture of the aldehyde (39) with the diester (38) and butyl 4(5)-hydroxymethylimidazole-5(4)-carboxylate (R_F 0.17, 0.45, and 0.02, respectively, on Al_2O_3 in 60 : 1 $CHCl_3$–MeOH), was washed with 2 : 1 benzene–light petroleum (b.p. 60—80°) (200 ml) and then with benzene (50 ml). Crystallisation of the residue (9.15 g), m.p. 181—187°, by concentration of a solution in hot ethyl acetate gave the pure *aldehyde* (39) (7.9 g), m.p. 190.5—192.5° (Found: C, 55.05; H, 6.3; N, 14.15. $C_9H_{12}N_2O_3$ requires C, 55.1; H, 6.15; N, 14.3%), *m/e* 196 (M^+), $\lambda_{max.}$ (EtOH) 276 nm (ε 9 700), δ($CDCl_3$–[$^2H_6$]DMSO) 0.95 (3 H, t, Me), 4.39 (2 H, t, CO_2CH_2Pr), 7.96 (1 H, s, N–CH=N), and 10.38 (1 H, s, CHO).

Butyl 4(5)-(6-*Carboxyhex*-1-*enyl*)*imidazole*-5(4)-*carboxylate* (40).—A solution of sodium methylsulphinylmethanide [from sodium hydride (1.6 g) and dimethyl sulphoxide (36 ml)] was added to a stirred mixture of the aldehyde (39) (2.58 g) with anhydrous (5-carboxypentyl)triphenylphosphonium bromide [26] (6.0 g) in dry dimethyl sulphoxide (5 ml) at room temperature. The resulting solution was set aside overnight, acidified with acetic acid, with cooling, diluted with water (300 ml), and basified with sodium carbonate, to give crystals (1.2 g) of triphenylphosphine oxide. The aqueous filtrate was saturated with carbon dioxide, filtered (Hyflo), and acidified with acetic acid, and the liberated carboxylic acids were extracted into chloroform; the chloroform solution was washed with water, dried (Na_2SO_4), and evaporated. Crystallisation of the residual gum from

* Hoffmann *et al.*[25] obtained this diester *via* the di(acid chloride) in 43% yield.

ethyl acetate yielded (5-carboxypentyl)diphenylphosphine oxide (1.46 g), m.p. 137—139°; concentration of the liquors gave more solid which was washed with 1,2-dichloroethane (3 × 12 ml), to leave a mixture (0.695 g), m.p. 123—127°, of the *E*- and *Z*-forms of the *carboxylic acid* (40). A recrystallised (EtOAc) sample had m.p. 126—129° (Found: C, 60.85; H, 7.6; N, 9.3. $C_{15}H_{22}N_2O_4$ requires C, 61.2; H, 7.55; N, 9.5%), δ($CDCl_3$–[$^2H_6$]DMSO) 2.29 (2 H, t, CH_2CO_2H), 4.27 (2 H, t, CO_2CH_2Pr), 5.74 (double t, =CH–CH_2, *Z*-isomer), 6.46 (double t, =CH–CH_2, *E*-isomer), 6.87 (m, –CH=CH–, *Z*- and *E*-isomers), 7.56 (s, N–CH=N, *E*-isomer) and 7.62 (s, N–CH=N, *Z*-isomer). The ^1H n.m.r. data indicated a *Z* : *E* ratio of 2.1 : 1.

Butyl 4(5)-(6-Carboxyhexyl)imidazole-5(4)-carboxylate (41).—A solution of the mixed carboxylic acids (40) (0.65 g) in dilute aqueous sodium carbonate (25 ml) was added to a pre-reduced suspension of 5% palladium–charcoal (0.5 g) in water (25 ml) and shaken under hydrogen [uptake 54 ml (24 °C and 755 mmHg) during 70 min]. The filtered solution was acidified with acetic acid and the precipitated solid collected; crystallisation from ethyl acetate gave the *carboxylic acid* (41) (0.53 g), m.p. 129—130° (Found: C, 60.9; H, 8.3; N, 9.55. $C_{15}H_{24}N_2O_4$ requires C, 60.8; H, 8.15; N, 9.45%), δ($CDCl_3$–[$^2H_6$]DMSO) 2.15 (2 H, t, CH_2CO_2H), 2.80 (2 H, t, =$C(CH_2)$N), 4.15 (2 H, t, CO_2CH_2Pr), 7.43 (1 H, s, N–CH=N) and 9.3br (2 H, NH and CO_2H).

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