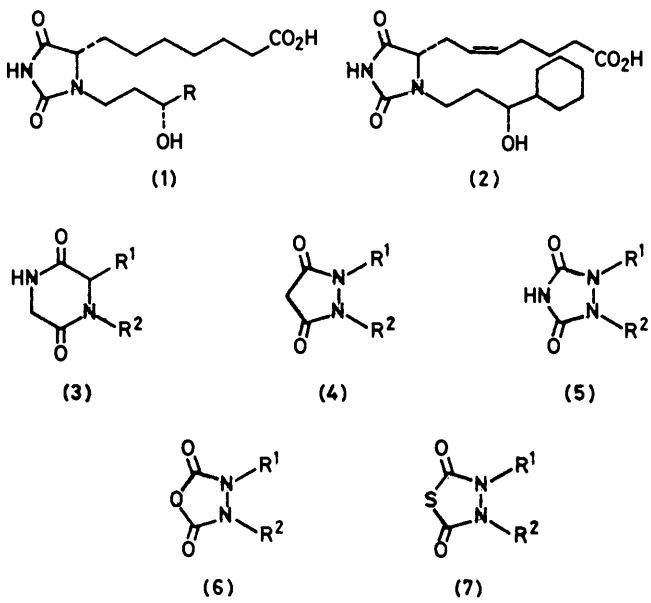
Heterocyclic Prostaglandin Analogues. Part 4.[1] Piperazine-2,5-diones, Pyrazolidine-3,5-diones, 1,2,4-Triazolidinediones, 1,3,4-Oxadiazolidinediones and 1,3,4-Thiadiazolidinediones

By **Paul Barraclough, A. Gordon Caldwell, C. John Harris, and Norman Whittaker,*** The Wellcome Research Laboratories, Beckenham, Kent BR3 3BS

Piperazinedione prostaglandin analogues (10) have been prepared from the previously described di-substituted glycine esters (8). The corresponding pyrazolidinediones (27) and triazolidinediones (30) were obtained by multi-step synthesis from ethyl carbazate (19) *via* the common intermediates (23). An oxadiazolidinedione (37) and a thiadiazolidinedione (40b) are also described. The piperazinedione (10c) and the triazolidinedione (30c) have *ca.* one-tenth of the anti-aggregatory potency of prostaglandin E_1. Some structure–activity relationships have emerged.

THE synthesis and biological properties of heterocyclic prostaglandin (PG) analogues containing a pyrrolidinedione [2] or hydantoin [1,3] ring have recently been reported from this laboratory. Particularly noteworthy were the hydantoins (±)-(1; R = alkyl, branched alkyl, cycloalkyl), and especially (±)-(1; R = cyclohexyl) and (±)-(2) which have, respectively, about 14 and 22 times the

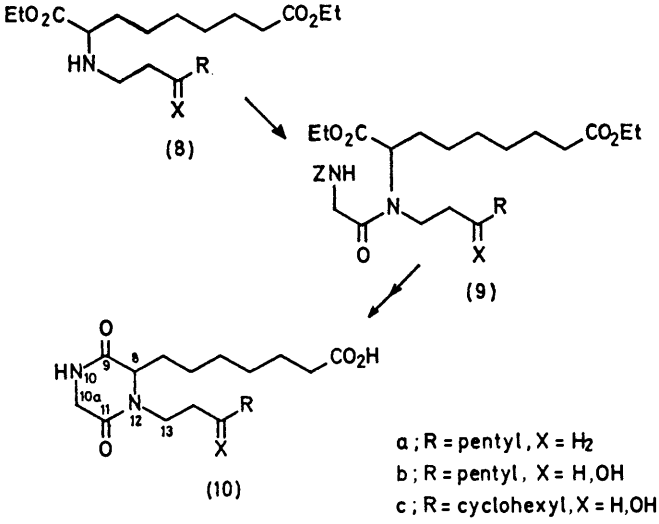


potency of PGE_1 as inhibitors of platelet aggregation coupled with selectivity of biological action. Since this high activity is confined to the isomers in which the relative stereochemistry at the two centres of asymmetry corresponds to that in the natural platelet aggregation inhibitors, such as PGE_1 and PGD_2, it was concluded that their mode of action is similar. By synthesis of further heterocyclic PG analogues of types (3)—(7),† we have now identified the structural features of amide-based rings which are important for high activity.

† All the analogues described here were synthesised as racemic compounds.

RESULTS AND DISCUSSION

To assess the feasibility of synthesis of piperazine-2,5-diones starting from glycine esters bearing PG-type side chains, the previously described [2,3b] intermediate (8a) was condensed with Cbz-glycine in the presence of *NN'*-dicyclohexylcarbodi-imide (DCC) (Scheme 1). On reductive debenzylation of the resulting urethane (9a), the desired cyclisation occurred spontaneously to give the piperazinedione carboxylic ester which, on hydrolysis, afforded the model compound (10a). The above reaction sequence was then applied to the hydroxyoctyl intermediate (8b),[2,3] without protection of the hydroxyl function, to give the piperazinedione PG analogue (10b) as a separable (h.p.l.c.) mixture of diastereoisomers. The cyclohexyl variant (10c) was synthesised in a similar way, except that the preferred route to the urethane (9c) was by condensation of the intermediate (8c) with the

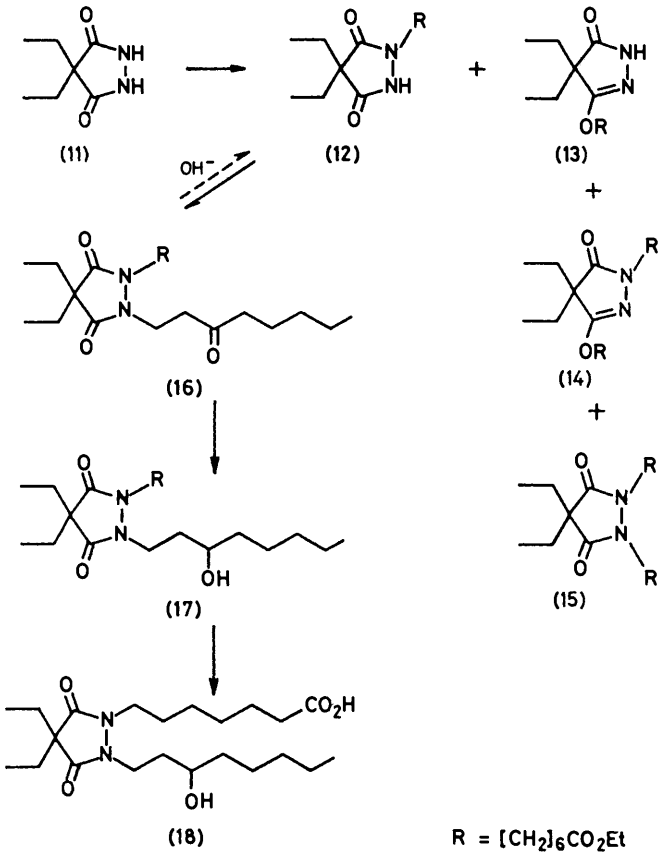


SCHEME 1

mixed anhydride derived from Cbz-glycine and ethyl chloroformate, and it too was obtained as a mixture of two separable (h.p.l.c.) diastereoisomers. Neither diastereoisomer of (10b) had appreciable anti-aggregatory activity, nor had the more polar diastereoisomer of (10c).

In contrast, the less polar diastereoisomer of (10c) had one-tenth of the anti-aggregatory potency of PGE_1 in human platelet-rich plasma. The less polar diastereoisomer also differed from the more polar in exhibiting a greater degree of magnetic non-equivalence for the C-13 protons.* Thus, the correlation of chromatographic polarity with n.m.r. characteristics and biological potency previously observed [3] for the diastereoisomers of hydantoin PG analogues also holds for the corresponding piperazinediones.

In our initial approach (Scheme 2) to pyrazolidine-3,5-



SCHEME 2

dione PG analogues, we investigated *N*-alkylation of the readily accessible 4,4-diethylpyrazolidine-3,5-dione (11) rather than the parent heterocycle which, it was anticipated, would undergo *C*-alkylation preferentially. Treatment of (11) with ethyl 7-bromoheptanoate (1 equiv.) in alcoholic sodium ethoxide gave a mixture of neutral and acidic products. Separation of the neutral products by column chromatography afforded the *O*-alkylated, *NO*-dialkylated, and *NN'*-dialkylated species (13), (14), and (15), respectively, whereas the acidic fraction gave the required *N*-alkylated compound (12). Michael-type addition of (12) to pentyl vinyl ketone produced the adduct (16), which was converted *via* the hydroxyoctyl compound (17) into the carboxylic acid (18) by successive treatment with sodium borohydride and aqueous alcoholic alkali. An attempt to carry out the last two steps in the reverse order was unsuccessful since exposure of the adduct (16) to alkali resulted in loss of the oxo-octyl moiety. The pyrazolidinedione (18) had no significant anti-aggregatory activity.

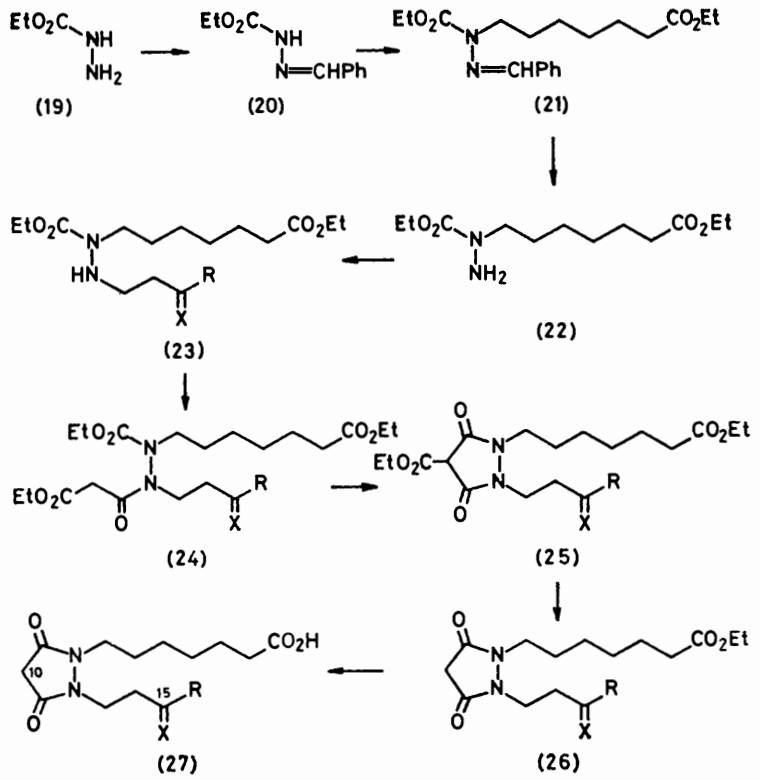
Synthesis of pyrazolidine-3,5-dione PG analogues unsubstituted at C-10 followed the strategy adopted in our earlier syntheses of pyrrolidinedione [2] and hydantoin [3] PG analogues and called for the provision of acyclic intermediates with pre-formed PG-type side-chains, suitable for elaboration to the target heterocycle. Accordingly a route to the di-substituted carbazates (23) was first investigated (Scheme 3). The benzylidene group has been used [4] to protect the primary amino-function of ethyl carbazate (19) and, at the same time, to provide activation for reaction at the urethane NH; in our hands, alkylation of the sodium salt of ethyl benzylidenecarbazate (20) with ethyl 7-bromoheptanoate proceeded smoothly in the presence of hexamethylphosphoric triamide to give the di-ester (21). The benzylidene moiety was removed by catalytic hydrogenation to the corresponding benzyl compound and subsequent hydrogenolysis, to give the mono-substituted carbazate (22) in excellent yield; the latter was also obtainable, but in unexpectedly poor yield, by acid-catalysed solvolysis of (21). The 3-octylcarbazate (23a), obtained from (22) by alkylation with octyl iodide or, more efficiently, by reductive alkylation with octanal, was condensed with monoethyl malonate in the presence of DCC to give the malonamide (24a). Cyclisation of (24a) was readily achieved in refluxing ethanolic sodium ethoxide and the resulting ethoxycarbonylpyrazolidinedione (25a) readily underwent partial hydrolysis and decarboxylation in refluxing moist acetonitrile, yielding the ester (26a).† Saponification of (26a) gave the carboxylic acid (27a) in 60% overall yield from (23a).

Michael-type addition of the carbazate (22) to pentyl vinyl ketone or cyclohexyl vinyl ketone proceeded slowly to give the mono-adducts (23b) and (23d), respectively, together with significant amounts of the bis-adducts. This behaviour contrasts with that of the more basic ‡ diethyl 2-aminononanedioate,[3] where the addition is more rapid and, apparently, more easily reversed. Reduction of the mono-adduct (23b) with sodium borohydride gave the corresponding alcohol (23c) but *N*-acylation of the latter with monoethyl malonate as above was of little preparative value due to competing *O*-acylation. That problem was circumvented, however, by acylation of the ketone (23b) to give (24b), followed by reduction to the required hydroxy-compound (24c), which was readily converted *via* intermediates (25c) and (26c) into the pyrazolidinedione (27c). Application of the same reaction sequence to the mono-adduct (23d) led to the cyclohexyl analogue (27e). These PG analogues, unlike the related hydantoins (1),

* Prostanoic acid numbering is used throughout the Discussion.

† This mild procedure appears to be more convenient than previously reported syntheses [5] of simple pyrazolidine-3,5-diones.

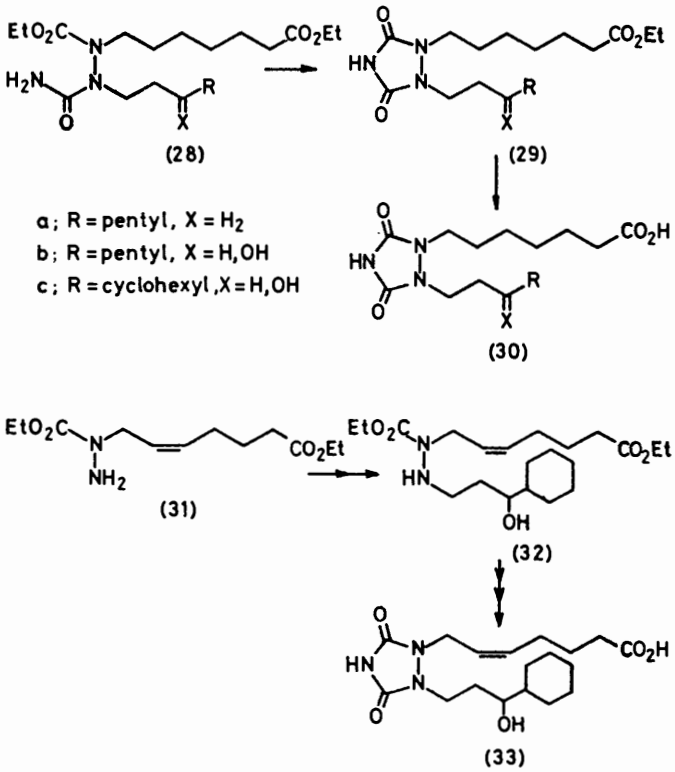
‡ Inferred from the pK_a values of 3.5 and 7.7 for the conjugate acids of ethyl carbazate and glycine ethyl ester, respectively.



SCHEME 3

have only one centre of asymmetry and are thus obtained as a single racemate. The hydroxyoctyl compound (27c) did not have significant anti-aggregatory activity whereas the cyclohexyl analogue (27e) had one-hundredth of the potency of PGE_1 in human platelet-rich plasma.

The carbazates (23) are also useful intermediates for the preparation of novel PG analogues based on other ring systems. For example, reaction of compound (23a) with cyanic acid gave the carbamoylcarbazate (28a) (Scheme 4) which cyclised on being heated [6] in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) to give the 1,2,4-triazolidinedione (urazole) ester (29a); saponification with aqueous base then gave the carboxylic acid (30a). Similarly, the hydroxyoctylurazole (30b) and the cyclohexyl analogue (30c) were obtained * *via* the intermediates (28b) and (28c), respectively. For the synthesis of the 5,6-didehydro-species (33) (Scheme 4), the required mono-substituted carbazate (31) was prepared by alkylation of the Schiff base (20) with methyl (*Z*)-7-bromohept-5-enoate followed by acid-catalysed solvolysis of the benzylidene residue in aqueous ethanol. Sequential reaction of (31) with cyclohexyl vinyl ketone and sodium borohydride then furnished the di-sub-



SCHEME 4

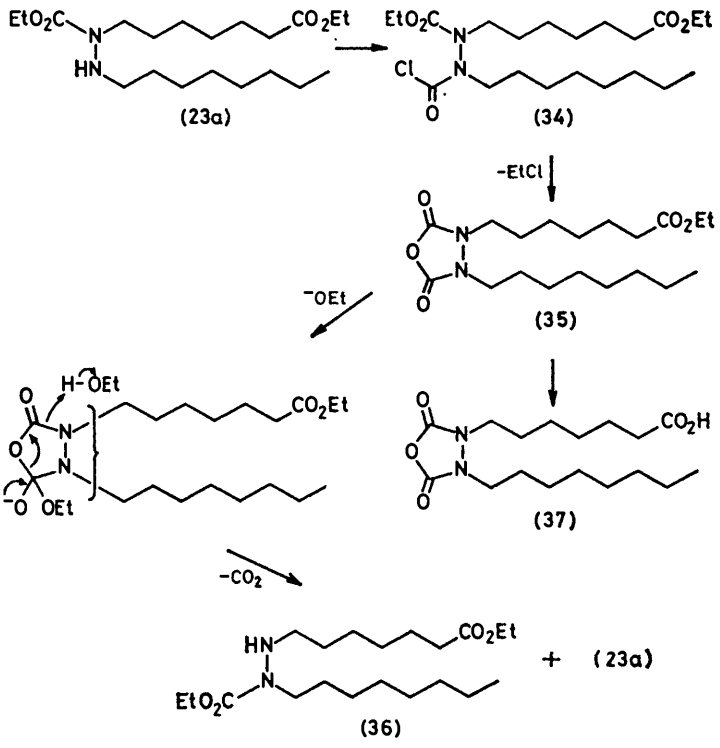
* Urazole PG analogues with a substituent at *N*-10 have been obtained by the Beecham group [7] by bis-alkylation of 4-alkylurazoles. The 10-unsubstituted analogue (30b) has also been prepared in our laboratory using similar methods, to be reported elsewhere.

stituted carbazate (32) which was converted, in the manner described above, into the urazolecarboxylic acid (33). The hydroxyoctylurazole (30b) had only weak anti-aggregatory activity but the cyclohexyl analogue (30c) and its 5,6-didehydro derivative (33) had, respectively, one-eighth and one-twentieth of the potency of PGE_1.

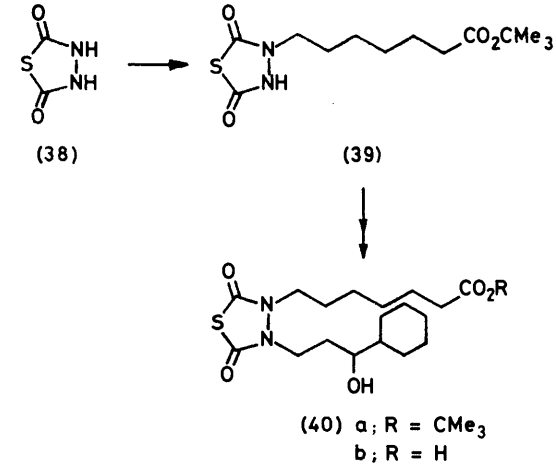
The 1,3,4-oxadiazolidinedione system has also been investigated. Reaction of the carbazate (23a) with phosgene gave the carbamoyl chloride (34) which, on pyrolysis,[8] afforded (Scheme 5) the oxadiazolidinedione ester (35). Attempted saponification of (35) with aqueous ethanolic alkali led, not surprisingly, to fission of the ring, to give a presumed mixture of the carbazates (23a) and (36), probably by the mechanism indicated. The required carboxylic acid (37) was, however, obtained by reaction of (35) with iodotrimethylsilane.[9] As yet, the chemistry of the 1,3,4-oxadiazolidinedione ring system has received scant attention. Our investigations have shown that cleavage of the ring takes place rapidly on exposure of (37) to aqueous sodium hydrogencarbonate; experiments with another model compound reveal that cleavage also occurs on treatment with sodium borohydride.* In view of the inherent lability of this heterocycle to those types of reagent, synthesis of 15-hydroxy PG analogues was therefore not attempted.

Following procedures developed by Du Pont investigators,[10] the novel 1,3,4-thiadiazolidinedione PG analogue (40b) has now been prepared (Scheme 6) from the parent heterocycle (38). Interestingly, it proved to be more stable to hydrolysis than the related 1,3,4-oxadiazolidinedione (37). It had one-hundredth of the anti-aggregatory potency of PGE_1.

Structure–Activity Relationships.—The differences in anti-aggregatory potency between the hydantoin (±)-(1; R = cyclohexyl) and the analogues described above cannot be attributed to differential binding to other components of plasma, such as serum albumin, since experiments with washed platelets have given similar results. It can therefore be concluded that hydantoin (±)-(1; R = cyclohexyl) binds to human platelet



SCHEME 5



SCHEME 6

* From 3-benzyl-4-(6-ethoxycarbonylhexyl)-1,3,4-oxadiazolidine-2,5-dione, the only isolable product was a mixture of two *N*-formyl compounds.

receptors more than one hundred times more effectively than the corresponding urazole (30c) or piperazinedione (10c; less polar isomer), and about one thousand times more effectively than the corresponding pyrazolidinedione (27e) and thiadiazolidinedione (40b). At the pH (7.2) of human platelet-rich plasma, the degree of ionisation of the hetero-ring in the hydantoin, urazole, and pyrazolidinedione compounds is estimated * to be 1, 20, and 60%, respectively. For those species, therefore, it is inferred that receptor binding is associated with the unionised form of the ring.†

The fact that only one of the piperazinedione diastereoisomers has substantial anti-aggregatory activity indicates that the relative disposition of the side chains resulting from the presence of a chiral centre at C-8 plays an important role in receptor binding. For five-membered heterocycles it is also apparent that replacement of CH_2 or S (or NMe †) at position 10 by NH considerably enhances receptor binding. It would appear that it is the assembly of both of those features in a single molecule that gives the hydantoin its unique binding affinity for platelet receptors and, thereby, its outstanding anti-aggregatory activity.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in deuteriochloroform unless otherwise stated, using a Bruker HFX-90 or a Varian HA-100 spectrometer; proton couplings were 7 Hz except where cited. I.r. spectra for liquids relate to thin films. Mass spectra (e.i.) were obtained on an A.E.I. MS902 spectrometer, interfaced to a VG MULTISPEC data system, at 70 eV.

6-(6-*Carboxyhexyl*)-1-*octylpiperazine*-2,5-*dione* (10a).—A solution of diethyl 2-octylaminononanedioate [2] (8a) (3.71 g, 0.01 mol) and *N*-benzyloxycarbonylglycine (2.29 g, 0.011 mol) in dichloromethane (20 ml) was cooled in ice and stirred during the gradual addition of dicyclohexylcarbodi-imide (2.26 g, 0.011 mol). After stirring for 1.25 h at room temperature, the resulting crystals of dicyclohexylurea (2.12 g) were collected and the filtrate was evaporated to dryness. The residual oil was dissolved in ether and the solution was washed with 1N-hydrochloric acid, then with 1N-aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and evaporated to leave crude diethyl 2-(*N*-benzyloxycarbonylglycyl-*N*-octylamino)nonanedioate (6.6 g). This material, dissolved in ethanol (27 ml) and glacial acetic acid (3 ml), was treated with 10% palladium–charcoal (740 mg) and a stream of hydrogen was passed through the stirred mixture until carbon dioxide was no longer present in the issuing gas (*ca.* 7 h). After removal of the catalyst, the solvent was evaporated, water was added and the mixture was basified with 1N-aqueous sodium hydroxide. The insoluble oil was extracted into ether and the extract was washed with water, dried ($MgSO_4$), and evaporated to leave impure 6-(6-ethoxycarbonylhexyl)-1-octylpiperazine-2,5-dione ‡ (4.68 g). The ester was hydrolysed by stirring for 1 h in a mixture of ethanol (18 ml) and 2N-aqueous sodium hydroxide (9.2 ml); the alcohol was evaporated, water was added and the suspension was washed with ether. The aqueous solution was acidified with 2N-hydrochloric acid, the liberated carboxylic acid was extracted into chloroform, and the washed and dried extract was evaporated to give an oil. Treatment of the oil with a little ether gave crystals (2.1 g) of 6-(6-*carboxyhexyl*)-1-*octylpiperazine*-2,5-*dione* which crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) in colourless plates, m.p. 114—115 °C (Found: C, 64.65; H, 10.05; N, 7.65. $C_{19}H_{34}N_2O_4$ requires C, 64.4; H, 9.65; N, 7.9%).

1-(6-*Carboxyhexyl*)-6-*octylpiperazine*-2,5-*dione*.—This acid, isomeric with the above, was prepared by a similar series of reactions, starting with ethyl 2-(6-ethoxycarbonylhexylamino)decanoate.[3b] The *carboxylic acid* formed colourless prisms (from EtOAc), m.p. 103—104 °C (Found: C, 64.4; H, 9.7; N, 7.95%).

6-(6-*Carboxyhexyl*)-1-(3-*hydroxyoctyl*)*piperazine*-2,5-*dione* (10b).—The crude product obtained from reaction of diethyl 2-(3-hydroxyoctylamino)nonanedioate [2] (8b) (7.74 g) with *N*-benzyloxycarbonylglycine (4.6 g) in dichloromethane (90 ml) in the presence of dicyclohexylcarbodi-imide (4.53 g), under conditions similar to those described above, was freed from a less polar impurity (probably *NO*-diacylated material) by chromatography [SiO_2; $CHCl_3$–EtOAc (9 : 1)]. The resulting nearly pure glycinamide (9b) was a colourless oil (6.4 g); δ 0.89 (3 H, t, CH_2CH_2Me), 1.17 (6 H, t, 2 × OCH_2Me), *ca.* 1.8 (1 H, br, OH), 2.28 (2 H, t, CH_2CO_2Et), *ca.* 3.6 (3 H, m, $CONCH_2$ and CHOH), 4.12 and 4.2 (7 H, m, 2 × OCH_2Me, $NHCH_2CO$, and $CONCHCO_2Et$), 5.11 and 5.12 (each 1 H, s, $PhCH_2$), *ca.* 5.8 (1 H, NH), and 7.37 (5 H, s, aromatic protons). This material (2.9 g), dissolved in ethanol (26.1 ml) and glacial acetic acid (2.9 ml), was treated with hydrogen in the presence of palladium–charcoal catalyst as described above to give 6-(6-ethoxycarbonylhexyl)-1-(3-hydroxyoctyl)piperazine-2,5-dione (1.45 g) as a solid, m.p. 65—80 °C, consisting of a mixture of diastereoisomers, R_F 0.54 and 0.63 [SiO_2; $CHCl_3$–MeOH (9 : 1)]. The foregoing ester (1.6 g) was stirred in 1N-aqueous sodium hydroxide (6 ml) for 1.5 h and the acidic product was isolated as described above, to give the *carboxylic acid* (10b) (1.09 g), R_F 0.53 and 0.60 [SiO_2; $CHCl_3$–MeOH–HOAc (90 : 5 : 5)]. The diastereoisomers were separated by h.p.l.c. to give the *less-polar diastereoisomer* as colourless plates [from ethyl acetate–light petroleum (b.p. 60—80 °C)] m.p. 102—104 °C (Found: C, 61.95; H, 9.55; N, 7.45. $C_{19}H_{34}N_2O_5$ requires C, 61.6; H, 9.25; N, 7.55%), δ 0.89 (3 H, t, Me), 2.32 (2 H, t, CH_2CO_2H), 2.95 (1 H, m, one chain-NCH_2 proton), 3.52 (1 H, m, CHOH), 3.88, 3.99, and 4.09 (4 H, m, NCH, ring-NCH_2 and one chain-NCH_2 proton), 5.1 (2 H, br, OH and CO_2H), and 6.7 (1 H, br, s, NH): and the *more-polar diastereoisomer* as colourless prisms (from EtOAc), m.p. 102—104 °C (Found: C, 61.35; H, 9.5; N, 7.4%); δ 0.91 (3 H, t, Me), 2.34 (2 H, t, CH_2CO_2H), *ca.* 3.3, 3.6, and 3.8 (3 H, m, one chain-NCH_2 proton, CHOH, and one chain-NCH_2 proton), 3.92 and 4.00 (3 H, m, NCH and ring-NCH_2), 5.9 (2 H, br, OH and CO_2H), and 6.8 (1 H, br, s, NH).

6-(6-*Carboxyhexyl*)-1-(3-*cyclohexyl*-3-*hydroxypropyl*)*piperazine*-2,5-*dione* (10c).—To a stirred, cooled (−5 °C) solution

* Based on pK_a' values of 9.31, 7.79, and 7.02 for (±)-(1; R = cyclohexyl), (30c) and (27e), respectively, measured at 25° C in H_2O–EtOH (98 : 2) at an ionic strength of 5×10^{-3} mol dm^{-3}. A nitrogen pK_a' was not detected for the piperazinedione over the pH range 2—12.

† The N(10)-methylhydantoin (manuscript in preparation) is also active, having one-third of the anti-aggregatory potency of PGE_1.

‡ I.r. data supported this structural assignment, the ratio of amide : ester signals for the crude product being much greater than that in the benzyloxycarbonyl precursor.

of *N*-benzyloxycarbonylglycine (2.09 g) and triethylamine (1.01 g) in dry tetrahydrofuran (30 ml) was added dropwise a solution of ethyl chloroformate (1.09 g) in tetrahydrofuran (5 ml). After a further 15 min, a solution of diethyl 2-(3-cyclohexyl-3-hydroxypropylamino)nonanedioate [3b] (8c) (3.99 g) in tetrahydrofuran (5 ml) was added dropwise and the mixture was stirred at room temperature for 4 h. The solvent was evaporated, water and chloroform were added, and the chloroform phase was washed with dilute hydrochloric acid, then with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and evaporated, to leave the crude glycinamide (9c) as a yellow oil (6.36 g). Hydrogenolysis of this material as described above gave the piperazinedione ester as an oil (3.2 g), a portion (2.3 g) of which was hydrolysed with aqueous alcoholic sodium hydroxide to give the *carboxylic acid* (10c) (1.4 g), R_F 0.40 and 0.46 [SiO_2; $CHCl_3$–MeOH–HOAc (90 : 5 : 5)]. Separation by h.p.l.c. gave the individual diastereoisomers; the *less-polar* as small needles (from EtOAc), m.p. 132—134 °C (Found: C, 63.1; H, 9.3; N, 7.45. $C_{20}H_{34}N_2O_5$ requires C, 62.8; H, 8.95; N, 7.3%), δ ($CDCl_3$–[$^2H_6$]DMSO) 2.24 (2 H, t, CH_2CO_2H), 2.98 and 3.24 (2 H, m, one chain-NCH_2 proton and CHOH), 3.86, 3.90, and 4.00 (4 H, m, NCH, ring-NCH_2, and one chain-NCH_2 proton), 4—5 (2 H, vbr, OH and CO_2H), and 7.35 (1 H, br, s, NH): and the *more-polar* as small needles (from EtOAc), m.p. 128—130 °C (Found: C, 62.9; H, 9.25; N, 7.25%); δ ($CDCl_3$–[$^2H_6$]-DMSO) 2.25 (2 H, t, CH_2CO_2H), *ca.* 3.2 and 3.3 (2 H, m, one chain-NCH_2 proton and CHOH), 3.67, 3.86, and 3.91 (4 H, m, one chain-NCH_2 proton, NCH, and ring-NCH_2), and 7.2 (1 H, br, s, NH) (resonances of OH and CO_2H too broad to be visible).

Alkylation of 4,4-*Diethylpyrazolidine*-3,5-*dione with Ethyl* 7-*Bromoheptanoate*.—To a solution of sodium ethoxide [from sodium (4.6 g) and ethanol (200 ml)] was added 4,4-diethylpyrazolidine-3,5-dione [11] (40 g); the suspension was stirred for 15 min, ethyl 7-bromoheptanoate (47.4 g) was added, and the mixture was refluxed for 4 h. After cooling, the solid was filtered off; the filtrate was evaporated to dryness, the residue was treated with water (200 ml), and the mixture was brought to pH 9 with 2N-aqueous sodium hydroxide and shaken with ether [see (A) below]. The clear aqueous phase was separated and immediately acidified with 2N-hydrochloric acid to precipitate an oil which was extracted into ether. The washed and dried ($MgSO_4$) ethereal solution was evaporated to leave a pale yellow oil (19.1 g) which was freed from unchanged diethylpyrazolidinedione by chromatography (SiO_2; $CHCl_3$), to give 1-(6-*ethoxycarbonylhexyl*)-4,4-*diethylpyrazolidine*-3,5-*dione* (12) as a colourless oil (11.5 g) which could be distilled with only slight decomposition, b.p. 184—186 °C/0.01 mmHg, n_D^{17} 1.4781 (Found: C, 61.25; H, 8.8; N, 8.75. $C_{16}H_{28}N_2O_4$ requires C, 61.5; H, 9.05; N, 8.95%); $\nu_{max.}$ 1 750 (ester), and 1 750 and 1 680 cm^{-1} (pyrazolidinedione); δ 0.81 (6 H, t, 2 × CH_2Me), 2.26 (2 H, t, CH_2CO_2Et), 3.60 (2 H, t, NCH_2), and 4.08 (2 H, q, OCH_2Me).

The ethereal washing (A) was washed with 1N-aqueous sodium hydroxide then water, dried, and evaporated, to leave an oil (25.8 g) which was distilled, first at 16 mmHg to remove unchanged bromo-ester, and then at 0.05 mmHg to give fractions of b.p. ranging from 165 to 215 °C. Chromatography [neutral Al_2O_3; $CHCl_3$–benzene (1 : 1)] of the lower-boiling fractions (2.0 g) gave 3-(6-*ethoxycarbonylhexyloxy*)-4,4-*diethylpyrazol*-5-*one* (13) (700 mg) as a colourless oil, R_F 0.25 (SiO_2; $CHCl_3$) (Found: C, 61.9; H, 9.1; N, 8.95. $C_{16}H_{28}N_2O_4$ requires C, 61.5; H, 9.05; N, 8.95%); $\nu_{max.}$ 1 740 (ester), and 1 720 and 1 620 cm^{-1} (pyrazolone). Chromatography (neutral Al_2O_3; benzene) of the higher-boiling fractions (6.7 g) yielded a colourless oil (4.5 g), R_F 0.48 (SiO_2; $CHCl_3$) but R_F 0.7 and 0.75 [SiO_2; Et_2O–Pr^i_2O–HOAc (70 : 35 : 3)], which was separable by h.p.l.c. [SiO_2; EtOAc–hexane–HOAc (40 : 59 : 1); u.v. monitoring at 300 nm] to give the more-polar species, 1,2-*bis*-(6-*ethoxycarbonylhexyl*)-4,4-*diethylpyrazolidine*-3,5-*dione* (15) (Found: C, 63.9; H, 9.25; N, 5.75. $C_{25}H_{44}N_2O_6$ requires C, 64.05; H, 9.45; N, 6.0%); δ 0.77 (6 H, t, 2 × CH_2Me), 2.25 (4 H, t, 2 × CH_2CO_2Et), 3.56 (4 H, t, 2 × NCH_2), and 4.08 (4 H, q, 2 × OCH_2Me): and the less-polar 1-(6-*ethoxycarbonylhexyl*)-3-(6-*ethoxycarbonylhexyloxy*)-4,4-*diethylpyrazol*-5-*one* (14) (Found: C, 64.0; H, 9.6; N, 5.7%); δ 0.70 (6 H, t, 2 × CH_2Me), 2.26 and 2.27 (each 2 H, t, 2 × CH_2CO_2Et), 3.55 (2 H, t, NCH_2), and 4.09, 4.13, and 4.14 (6 H, m, 2 × OCH_2Me and $CH_2OC{=}N$).

1-(6-*Ethoxycarbonylhexyl*)-4,4-*diethyl*-2-(3-*hydroxyoctyl*)-*pyrazolidine*-3,5-*dione* (17).—A solution of 1-(6-ethoxycarbonylhexyl)-4,4-diethylpyrazolidine-3,5-dione (12) (5.5 g) and oct-1-en-3-one (4.5 g; 2 mol equiv.) in ethanol (35 ml) was treated with 2N-aqueous sodium hydroxide (0.5 ml) and refluxed for 1.25 h. 2N-Aqueous acetic acid (0.5 ml) was added, the alcohol was evaporated, and a solution of the residue in ether was washed with 1N-aqueous sodium hydroxide, then with water, dried ($MgSO_4$), and evaporated to leave a pale yellow oil * (9.0 g) consisting of the adduct (16), R_F 0.45 (SiO_2; $CHCl_3$), and unchanged oct-1-en-3-one, R_F 0.95.

The crude adduct (16) (7 g) was added gradually to a stirred, ice-cooled solution of sodium borohydride (700 mg) in ethanol (21 ml). After 30 min, the mixture was made weakly acidic by addition of 2N-sulphuric acid, water was added, and the insoluble oil was extracted into ether. The ethereal solution was washed with water, dried, and evaporated to leave a pale yellow oil (6.65 g) which was distilled to give the *hydroxy-ester* (17) as a colourless oil, b.p. 204—206 °C/0.01 mmHg, n_D^{20} 1.4768 (Found: C, 65.55; H, 10.3; N, 6.1. $C_{24}H_{44}N_2O_5$ requires C, 65.4; H, 10.05; N, 6.35%).

1-(6-*Carboxyhexyl*)-4,4-*diethyl*-2-(3-*hydroxyoctyl*)*pyrazolidine*-3,5-*dione* (18).—A solution of the hydroxy-ester (17) (3.0 g) in 2N-aqueous sodium hydroxide (3 ml) and ethanol (6 ml) was kept at room temperature for 1 h. Water was added and the mixture was washed with ether to remove some suspended unchanged ester; the aqueous solution was acidified, the liberated carboxylic acid was extracted into ether, and the washed and dried ether solution was evaporated to give the *hydroxy-acid* (18) (2.4 g). A portion was freed from traces of impurity by h.p.l.c. [SiO_2; CH_2Cl_2–MeOH–HOAc (40 : 1 : 0.1); monitoring at 290 nm)] to afford the pure acid (Found: C, 63.75; H, 10.1; N, 6.9. $C_{22}H_{40}N_2O_5$ requires C, 64.05; H, 9.75; N, 6.8%); δ 0.82 (3 H, t, Me) and 0.83 (6 H, t, 2 × Me), 2.34 (2 H, t, CH_2CO_2H), *ca.* 3.6 (4 H, m, NCH_2, CHOH, and one proton of non-equivalent NCH_2), and 4.0 (1 H, m, one proton of non-equivalent NCH_2).

Ethyl 2-(6-*Ethoxycarbonylhexyl*)*carbazate* (22).—Ethyl 3-benzylidenecarbazate (20) [4,12] (76.9 g, 0.40 mol) was added in portions to a stirred suspension of sodium hydride (80%

* On distillation of a portion, decomposition occurred to give an oil, b.p. 190 °C/0.01 mmHg, which consisted mainly of the starting pyrazolidinedione (12), R_F 0.2 (SiO_2; $CHCl_3$), and only a little of the adduct (16).

dispersion in mineral oil, 12.1 g, 0.4 mol) in dry tetrahydrofuran (650 ml) under dry nitrogen. After evolution of hydrogen had ceased, dry hexamethylphosphoramide (75 ml) and sodium iodide (62 g, 0.41 mol) were added, followed by ethyl 7-bromoheptanoate (96 g, 0.41 mol) in a little tetrahydrofuran, and the suspension was stirred at room temperature for 24 h, then refluxed for 6 h. The cooled mixture was poured into ice–water, the product was extracted into ethyl acetate and the combined extracts were dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by column chromatography [SiO_2; $CHCl_3$–EtOH (98 : 2)] to give *ethyl 3-benzylidene-2-(6-ethoxycarbonylhexyl)carbazate* (21) (82 g) as a pale yellow syrup, *m/e* 348 (M^+, $C_{19}H_{28}N_2O_4$); $\nu_{max.}$ 1 735, 1 705, 1 609, and 1 573 cm^{-1}; δ 1.18 and 1.31 (each 3 H, t, 2 × OCH_2Me), 1.30—1.65 (8 H, m, 4 × CH_2), 2.23 (2 H, t, CH_2CO_2Et), 4.10 (6 H, m, 2 × OCH_2 and NCH_2), 7.31 and 7.65 (5 H, m, aromatic protons), and 7.83 (1 H, s, CH=N). This syrup (25 g), dissolved in ethanol (250 ml), was agitated with 10% palladium–charcoal (3.33 g) under hydrogen (100 lb in^{-2}) for 17 h at room temperature and the filtered (Celite) solution was evaporated *in vacuo* to give *ethyl 2-(6-ethoxycarbonylhexyl)carbazate* (22) (16.8 g) as a colourless oil, b.p. 106—108 °C/0.01 mmHg, *m/e* 260 (M^+, $C_{12}H_{24}N_2O_4$); $\nu_{max.}$ 3 340, 3 220, 1 735, and 1 695 cm^{-1}; δ 1.27 (6 H, t, 2 × OCH_2Me), 1.0—1.80 (8 H, m, 4 × CH_2), 2.31 (2 H, t, CH_2CO_2Et), 3.40 (2 H, t, NCH_2), 3.90 (2 H, s, exch. D_2O, NH_2), and 4.18 (4 H, q, 2 × OCH_2Me).

Ethyl 2-(6-Ethoxycarbonylhexyl)-3-octylcarbazate (23a).—A mixture of the carbazate (22) (5.2 g, 20 mmol) with octanal (2.56 g, 20 mmol) in ethanol (120 ml) was shaken with 10% palladium–charcoal (0.8 g) under hydrogen at atmospheric pressure and room temperature until uptake ceased (*ca.* 6 h). The filtered (Celite) solution was evaporated *in vacuo* and the residue was distilled, yielding *ethyl 2-(6-ethoxycarbonylhexyl)-3-octylcarbazate* (23a) (5.2 g) as a colourless syrup, b.p. 164—168 °C/0.01 mmHg, *m/e* 372 (M^+, $C_{20}H_{40}N_2O_4$); $\nu_{max.}$ 3 300, 1 738, and 1 700 cm^{-1}; δ 0.86 (3 H, t, CH_2CH_2Me), 1.10—1.80 (26 H, m, 10 × CH_2 and 2 × OCH_2Me), 2.26 (2 H, t, CH_2CO_2Et), 2.82 (2 H, br, t, $NHCH_2$), 3.35 (2 H, t, EtO_2C–NCH_2), and 4.18 (4 H, q, 2 × OCH_2).

Direct alkylation of the carbazate (22) with octyl iodide in refluxing ethanol gave carbazate (23a) in 36% yield.

Ethyl 3-(Ethoxycarbonylacetyl)-2-(6-ethoxycarbonylhexyl)-3-octylcarbazate (24a).—A stirred solution of the carbazate (23a) (2.0 g, 5.38 mmol) and monoethyl malonate (0.775 g, 5.88 mmol) in dichloromethane (42 ml) was treated dropwise with dicyclohexylcarbodi-imide (1.18 g, 5.88 mmol) and the resulting suspension was stirred at room temperature for 18 h. The solid was collected, the filtrate was evaporated *in vacuo*, and a solution of the residue in ether was filtered and evaporated. Purification of the residual syrup by column chromatography [SiO_2; ether–hexane (7 : 3)] gave the *carbazate* (24a) (2.25 g, 86%) as a colourless oil; δ 0.87 (3 H, t, CH_2CH_2Me), 1.23 (3 H, t, OCH_2Me), 1.26 (6 H, t, 2 × OCH_2Me), 2.26 (2 H, t, $CH_2CH_2CO_2Et$), 3.3—3.6 (6 H, m, 2 × NCH_2 and EtO_2CCH_2CO), 4.07 (2 H, q, OCH_2Me), and 4.15 (4 H, q, 2 × OCH_2Me).

1-(6-Ethoxycarbonylhexyl)-2-octylpyrazolidine-3,5-dione (26a).—A solution of the carbazate (24a) (2.25 g, 4.63 mmol) in alcoholic sodium ethoxide [from sodium (110 mg, 4.78 mmol) and anhydrous ethanol (46 ml)] was refluxed for 20 h. The cooled solution was diluted with chloroform and washed successively with 2N-hydrochloric acid and water, and the organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give crude 4-ethoxycarbonyl-1-(6-ethoxycarbonylhexyl)-2-octylpyrazolidine-3,5-dione (25a) as a yellow gum (*ca.* 2.2 g). A solution of this gum in acetonitrile (100 ml) and water (2.2 ml) was refluxed for 2.5 h, cooled, and evaporated, and the residue purified by column chromatography [SiO_2; Et_2O–EtOH (24 : 1)] to give the *pyrazolidinedione* (26a) (1.0 g, 59%) as a colourless glass; δ 0.88 (3 H, t, CH_2CH_2Me), 1.26 (3 H, t, OCH_2Me), 2.30 (2 H, t, CH_2CO_2Et), 3.16 (2 H, s, ring-CH_2), 3.61 (4 H, t, 2 × NCH_2), and 4.14 (2 H, q, OCH_2Me).

1-(6-Carboxyhexyl)-2-octylpyrazolidine-3,5-dione (27a).—The pyrazolidinedione (26a) (736 mg, 2 mmol) was dissolved in 0.5N-aqueous sodium hydroxide (8.8 ml, 2.2 equiv.) and set aside at room temperature for 2 h. The solution was acidified with 2N-hydrochloric acid and the liberated product was extracted into and recovered from chloroform, then purified by column chromatography [SiO_2, Et_2O–MeOH (25 : 1)] to yield the *carboxylic acid* (27a) (250 mg, 44%) as waxy plates, m.p. 44—45 °C (Found: C, 63.6; H, 9.65; N, 8.25. $C_{18}H_{32}N_2O_4$ requires C, 63.55; H, 9.4; N, 8.25%); δ 0.89 (3 H, t, CH_2Me), 1.2—1.6 (20 H, m, 10 × CH_2), 2.35 (2 H, t, CH_2CO_2H), 3.14 (2 H, s, ring-CH_2), 3.59 (4 H, t, 2 × NCH_2) and 8.6 (1 H, br, CO_2H). From the less-polar fractions, some starting ester (110 mg) was recovered.

Reaction of the Carbazate (22) *with Vinyl Ketones.*—(*a*) A mixture of the carbazate (22) (7.8 g, 0.03 mol) with oct-1-en-3-one (3.78 g, 0.03 mol) was set aside at room temperature for 5 days. The resulting syrup, a mixture of the mono- and bis-adducts, R_F 0.55 and 0.63 [SiO_2; Et_2O–hexane (7 : 3)], respectively, was purified by chromatography to give *ethyl 2-(6-ethoxycarbonylhexyl)-3-(3-oxo-octyl)carbazate* (23b) (6.7 g, 58%) as a pale yellow oil; δ 0.90 (3 H, t, CH_2CH_2Me), 1.23 (3 H, t, OCH_2Me), 1.26 (6 H, t, 2 × OCH_2Me), 1.2—1.9 (14 H, m, 7 × CH_2), 2.26 (2 H, t, CH_2CO_2Et), 2.40 (2 H, t, $COCH_2Bu$), 2.51 (2 H, t, $NHCH_2CH_2CO$), 3.06 (2 H, t, $NHCH_2CH_2CO$), 3.28 (2 H, t, EtO_2C–NCH_2), 4.10 (2 H, q, OCH_2Me), 4.13 (2 H, q, OCH_2Me), and 4.50 (1 H, br, s, NH).

(*b*) Reaction of the carbazate (22) with 1-cyclohexylprop-2-en-1-one and work-up as in (*a*) afforded *ethyl 3-(3-cyclohexyl-3-oxopropyl)-2-(6-ethoxycarbonylhexyl)carbazate* (23d) (50%) as a pale yellow oil; δ 1.25 (3 H, t, OCH_2Me), 1.27 (3 H, t. OCH_2Me), 1.2—2.0 (18 H, m, 9 × CH_2), 2.29 (2 H, t, CH_2CO_2Et), 2.35 (3 H, m, $COCH<$ and CH_2CO), 3.08 (2 H, t, $NHCH_2$), 3.32 (2 H, t, EtO_2C–NCH_2), 4.12 (2 H, q, OCH_2Me), 4.16 (2 H, q, OCH_2Me) and 4.45 (1 H, br, s, NH): and *ethyl 3,3-bis-(3-cyclohexyl-3-oxopropyl)-2-(6-ethoxycarbonylhexyl)carbazate* (7%) as a colourless syrup; δ 1.26 (6 H, t, 2 × OCH_2Me), 1.2—2.0 (28 H, m, 14 × CH_2), 2.2—2.7 (8 H, m, 2 × $COCH<$, CH_2CO_2Et, and 2 × CH_2CO), 3.10 (6 H, m, 3 × NCH_2), 4.13 (2 H, q, OCH_2Me), and 4.16 (2 H, q, OCH_2Me).

Ethyl 2-(6-Ethoxycarbonylhexyl)-3-(3-hydroxyoctyl)carbazate (23c).—Sodium borohydride (320 mg, 8.6 mmol) in ethanol (40 ml) was added during 15 min to a stirred, ice-cooled solution of the oxo-octylcarbazate (23b) (3.0 g, 7.8 mmol) in ethanol (40 ml) and the mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo*, the residue was shaken with water and ether, and the ethereal phase was dried ($MgSO_4$) and evaporated. Purification of the residual syrup by column chromatography [SiO_2; Et_2O–hexane (4 : 1)] gave the *hydroxyoctylcarbazate* (23c) (2.05 g, 68%) as a pale yellow syrup, R_F 0.34 [SiO_2; $CHCl_3$–EtOH (98 : 2)]; δ 0.89 (3 H, t, CH_2CH_2Me), 1.23 (3 H, t, OCH_2Me), 1.26 (3 H, t, OCH_2Me), 1.2—1.7

(18 H, m, 9 × CH_2), 2.27 (2 H, t, CH_2CO_2Et), 2.7—3.8 (7 H, m, 2 × NCH_2, CHOH, and NH), 4.06 (2 H, q, OCH_2Me), and 4.11 (2 H, q, OCH_2Me).

Ethyl 3-(3-*Cyclohexyl*-3-*hydroxypropyl*)-2-(6-*ethoxycarbonylhexyl*)*carbazate* (23e).—This was obtained from the ketone (23d), by reduction with sodium borohydride in the preceding manner, as a colourless syrup, R_F 0.4 [SiO_2; $CHCl_3$–EtOH (98 : 2)]; $\nu_{max.}$ 3 450, 3 305, 1 736, and 1 698 cm^{-1}; δ 1.0—1.90 (21 H, m, 10 × CH_2 and CH), 1.22 (6 H, t, 2 × OCH_2Me), 2.25 (2 H, t, CH_2CO_2Et), 2.86—3.50 (5 H, m, 2 × NCH_2 and CHOH), and 4.15 (4 H, q, 2 × OCH_2Me).

1-(6-*Carboxyhexyl*)-2-(3-*hydroxyoctyl*)*pyrazolidine*-3,5-*dione* (27c).—Following the general method of synthesis described above for the octylpyrazolidinedione (27a), the oxo-octylcarbazate (23b) was converted sequentially *via* compounds (24b) (76%) and (24c) (50%), R_F 0.30 [SiO_2; Et_2O–hexane (17 : 1)], into the pyrazolidinediones (25c) and (26c). Ester hydrolysis of (26c) with aqueous alkali gave 1-(6-*carboxyhexyl*)-2-(3-*hydroxyoctyl*)*pyrazolidine*-3,5-*dione* (27c) as colourless prisms (from $CHCl_3$–hexane), m.p. 70—71 °C (Found: C, 60.7; H, 9.2; N, 7.8. $C_{18}H_{32}N_2O_5$ requires C, 60.65; H, 9.0; N, 7.85%); δ 0.88 (3 H, t, Me), 1.2—1.8 (18 H, m, 9 × CH_2), 2.34 (2 H, t, CH_2CO_2H), 3.20 (2 H, s, $COCH_2CO$), 3.55 (4 H, m, 2 × NCH_2), 4.01 (1 H, quintet, CHOH), and 5.8 (2 H, br, OH and CO_2H).

1-(6-*Carboxyhexyl*)-2-(3-*cyclohexyl*-3-*hydroxypropyl*)*pyrazolidine*-3,5-*dione* (27e).—Reaction of the (3-cyclohexyl-3-oxopropyl)carbazate (23d) with monoethyl malonate gave *ethyl* 3-(3-*cyclohexyl*-3-*oxopropyl*)-3-*ethoxycarbonylacetyl*-2-(6-*ethoxycarbonylhexyl*)*carbazate* (24d) as a colourless syrup; δ 1.24 (3 H, t, OCH_2Me), 1.27 (6 H, t, 2 × OCH_2Me), 1.0—2.0 (18 H, m, 9 × CH_2), 2.27 (2 H, t, CH_2CO_2Et), 2.80 (2 H, t, CH_2CO), 3.32 (2 H, m, EtO_2CCH_2CO), 3.3—3.7 (5 H, m, 2 × NCH_2 and COCH<), 4.06 (2 H, q, OCH_2Me), and 4.13 (4 H, q, 2 × OCH_2Me). Sodium borohydride reduction of (24d) gave *ethyl* 3-(3-*cyclohexyl*-3-*hydroxypropyl*)-3-(*ethoxycarbonylacetyl*)-2-(6-*ethoxycarbonylhexyl*)*carbazate* (24e) as a colourless syrup; δ 1.26 (3 H, t, OCH_2Me), 1.29 (6 H, t, 2 × OCH_2Me), 2.30 (2 H, t, CH_2CO_2Et), 3.9 (1 H, br, OH), 3.36 (2 H, m, EtO_2CCH_2CO), 4.14 (2 H, q, OCH_2Me), and 4.23 (4 H, q, 2 × OCH_2Me). Cyclisation of (24e) with sodium ethoxide followed by refluxing in moist acetonitrile afforded 1-(3-*cyclohexyl*-3-*hydroxypropyl*)-2-(6-*ethoxycarbonylhexyl*)*pyrazolidine*-3,5-*dione* (26e) as a colourless glass; δ 1.23 (3 H, t, OCH_2Me), 1.0—1.9 (21 H, m, 10 × CH_2 and CH), 2.26 (2 H, t, CH_2CO_2Et), 3.11 (2 H, s, $COCH_2CO$), 3.2—3.7 (4 H, m, 2 × NCH_2), 3.91 (1 H, m, CHOH), and 4.10 (2 H, q, OCH_2Me); δ_C 14.0 (OCH_2CH_3), 24.4, 26.0 (4 C), 26.6, 28.0, 28.3, 28.8, 30.8, 33.9 (CH_2CO_2Et), 36.4 ($COCH_2CO$), 40.3 (CH), 42.7 and 43.6 (2 × NCH_2), 60.0 (OCH_2CH_3), 72.6 (CHOH), 167.5 and 168.0 (2 × CON<), and 173.5 (CO_2Et). Treatment of (26e) with aqueous alkali yielded 1-(6-*carboxyhexyl*)-2-(3-*cyclohexyl*-3-*hydroxypropyl*)*pyrazolidine*-3,5-*dione* (27e) as colourless crystals (from $CHCl_3$–Et_2O–hexane), m.p. 65—67 °C (Found: C, 61.65; H, 8.95; N, 7.35. $C_{19}H_{32}N_2O_5$ requires C, 61.95; H, 8.7; N, 7.6%); δ 0.9—1.9 (21 H, m, 10 × CH_2 and CH), 2.32 (2 H, t, CH_2CO_2H), 3.17 (2 H, s, $COCH_2CO$), 3.2—3.7 (4 H, m, 2 × NCH_2), 3.93 (1 H, m, CHOH), and 6.2 (2 H, br, OH and CO_2H).

1-(6-*Carboxyhexyl*)-2-*octyl*-1,2,4-*triazolidine*-3,5-*dione* (30a).—A stirred solution of the carbazate (23a) (2.5 g; 6.7 mmol) in ethanol (20 ml) and 2N-hydrochloric acid (7 ml; 14 mmol) was cooled in an ice-bath and treated dropwise with potassium cyanate (1.1 g; 13.6 mmol) in water (4 ml). The reaction mixture was stirred at room temperature for 24 h, the solvent removed *in vacuo*, and the residue treated with water (50 ml); the oil was extracted into ether, the combined extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give crude ethyl 3-carbamoyl-2-(6-ethoxycarbonylhexyl)-3-octylcarbazate (28a) as a pale yellow syrup. This was heated with 1,5-diazabicyclo[5.4.0]undec-5-ene (2 drops) on the steam bath for 12 h, yielding crude 1-(6-ethoxycarbonylhexyl)-2-octyl-1,2,4-triazolidine-3,5-dione (29a) as a brown syrup (2.8 g) which was stirred with 2N-aqueous sodium hydroxide (28 ml) at room temperature for 3 h. Insoluble impurities were removed by washing thoroughly with ether and the clear aqueous solution was acidified with 2N-hydrochloric acid; the liberated carboxylic acid was extracted into ethyl acetate, the combined extract was dried ($MgSO_4$), and the solvent was removed *in vacuo* to leave a pale yellow solid. Crystallisation from ethyl acetate–hexane gave the *carboxylic acid* (30a) as colourless crystals (620 mg), m.p. 76—78 °C (Found: C, 59.9; H, 9.35; N, 12.3. $C_{17}H_{31}N_3O_4$ requires C, 59.8; H, 9.15; N, 12.3%); $\nu_{max.}$ (KBr) 3 470 br, 3 150 br, 1 720, and 1 695 cm^{-1}; δ 0.87 (3 H, t, Me), 1.10—1.80 (20 H, m, 10 × CH_2), 2.33 (2 H, t, CH_2CO_2H), 3.54 (4 H, t, 2 × NCH_2), and 9.0 (2 H, br, exch., CO_2H and NH).

1-(6-*Carboxyhexyl*)-2-(3-*hydroxyoctyl*)-1,2,4-*triazolidine*-3,5-*dione* (30b).—Following the general method of synthesis described above for compound (30a), the carbazate (23c) was converted into the crude triazolidinedione ester (29b) which, after saponification and purification by column chromatography [SiO_2; $CHCl_3$–MeOH (19 : 1)], gave the *carboxylic acid* (30b) as a colourless gum (400 mg, 42%), R_F 0.5 [SiO_2; $CHCl_3$–MeOH–HOAc (90 : 5 : 5)]; $\nu_{max.}$ 3 400 br, 3 150 br, 1 760, and 1 705 cm^{-1}; δ 1.00 (3 H, t, Me), 1.10—2.0 (18 H, m, 9 × CH_2), 2.40 (2 H, t, CH_2CO_2H), 3.30—4.25 (5 H, m, 2 × NCH_2 and CHOH), 6.0—7.0 (2 H, br, exch., CO_2H and NH).

1-(6-*Carboxyhexyl*)-2-(3-*cyclohexyl*-3-*hydroxypropyl*)-1,2,4-*triazolidine*-3,5-*dione* (30c).—By the above general method, the carbazate (23e) was converted into 1-(3-*cyclohexyl*-3-*hydroxypropyl*)-2-(6-*ethoxycarbonylhexyl*)-1,2,4-*triazolidine*-3,5-*dione* (29c), a sample of which was purified by preparative t.l.c. {R_F 0.4 [SiO_2; $CHCl_3$–EtOH (19 : 1)]} for characterisation. The colourless gum had *m/e* 397 (M^+, $C_{20}H_{35}N_3O_5$); $\nu_{max.}$ 3 440, 3 160, 1 764, and 1 720 cm^{-1}; δ 1.24 (3 H, t, OCH_2Me), 1.0—1.80 (21 H, m, 10 × CH_2 and CH), 2.28 (2 H, t, CH_2CO_2Et), 3.55 (5 H, m, 2 × NCH_2 and CHOH), 4.12 (2 H, q, OCH_2Me), and 4.90 (2 H, br, exch., NH and OH); δ_C 14.1 (OCH_2CH_3), 24.5, 26.0 (3 C), 26.6, 28.1, 28.5, 28.8, 31.0, 34.0 (CH_2CO_2Et), 41.5 and 44.2 (2 × NCH_2), 43.7 (CH), 60.1 (OCH_2CH_3), 72.5 (CHOH), 154.9 and 155.4 (2 × CON<), and 173.5 (CO_2Et). Saponification of the ester (29c) with 2N-aqueous sodium hydroxide and purification of the product by column chromatography [SiO_2; $CHCl_3$–MeOH (19 : 1)] followed by crystallisation from ethyl acetate–hexane gave the *carboxylic acid* (30c) as a colourless solid, m.p. 104—107 °C (Found: C, 58.75; H, 8.65; N, 11.25. $C_{18}H_{31}N_3O_5$ requires C, 58.5; H, 8.45; N, 11.35%); δ 1.0—2.0 (21 H, m, 10 × CH_2 and CH), 2.33 (2 H, t, CH_2CO_2H), 3.34—4.0 (5 H, m, 2 × NCH_2 and CHOH), and 6.3 (3 H, br, exch., CO_2H, OH, and NH).

Ethyl 2-[(Z)-6-*Ethoxycarbonylhex*-2-*enyl*]*carbazate* (31).—Ethyl 3-benzylidenecarbazate (20) (9.61 g, 50 mmol) was added in portions to a stirred suspension of sodium hydride (80% dispersion in mineral oil, 1.55 g, 52 mmol) in dry tetrahydrofuran (12.5 ml) under dry nitrogen. After

evolution of hydrogen had ceased, methyl (*Z*)-7-bromohept-5-enoate (11.4 g, 52 mmol) in dry tetrahydrofuran (25 ml) was added and the suspension was stirred at room temperature overnight, then refluxed for 6 h. The cooled mixture was poured into ice–water containing sodium dihydrogen phosphate (20 g), the product was extracted into ethyl acetate, the combined extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the residual oil by column chromatography (SiO_2; $CHCl_3$) gave *ethyl 3-benzylidene-2-[(Z)-6-methoxycarbonylhex-2-enyl]carbazate* (14.5 g) as a pale yellow syrup, *m/e* 332 (M^+, $C_{18}H_{24}N_2O_4$); $\nu_{max.}$ 1 735, 1 703, 1 608, and 1 572 cm^{-1}, δ 1.37 (3 H, t, OCH_2Me), 1.76 (2 H, m, $CH_2CH_2CH_2$), 2.29 (4 H, m, CH_2CO_2Me and $CH{=}CHCH_2CH_2$), 3.62 and 3.66 (together 3 H, each s, CO_2Me), 4.31 (2 H, q, CO_2CH_2Me), 4.56 (2 H, t, $NCH_2CH{=}CH$), 5.48 (2 H, m, $CH{=}CH$), 7.34 and 7.65 (5 H, m, aromatic protons), 7.74 and 7.76 (together 1 H, each s, CH=N). The integral pointed to a *syn* : *anti* isomer ratio of *ca.* 2 : 1. This syrup (14 g) was heated in ethanolic hydrogen chloride (12% w/v, 300 ml) under reflux for 24 h, the resulting dark solution was evaporated *in vacuo*, and the residual oil was purified by chromatography [SiO_2; $CHCl_3$–EtOH (98 : 2)], to give ethyl 2-[(Z)-6-*ethoxycarbonylhex-2-enyl*]*carbazate* (31) (4.5 g) as a colourless oil, b.p. 120—125 °C/0.02 mmHg, *m/e* 258 (M^+, $C_{12}H_{22}N_2O_4$); $\nu_{max.}$ 3 350, 3 220, 1 735, 1 700, and 1 630 cm^{-1}; δ 1.23 and 1.26 (each 3 H, t, 2 × OCH_2Me), 1.61 (2 H, m, $CH_2CH_2CH_2$), 2.20 (4 H, m, $CH{=}CHCH_2CH_2$ and CH_2CO_2Et), 3.82 (2 H, s, exch., NH_2), 4.05 (6 H, m, NCH_2 and 2 × OCH_2Me), and 5.50 (2 H, m, $CH{=}CH$).

1-[(Z)-6-*Carboxyhex-2-enyl*]-2-(3-*cyclohexyl-3-hydroxypropyl*)-1,2,4-*triazolidine-3,5-dione* (33).—A mixture of the carbazate (31) (1.6 g, 6.2 mmol) with 1-cyclohexylprop-2-en-1-one (0.86 g, 6.2 mmol) was set aside at room temperature for 6 days. The resulting syrup was purified by chromatography [SiO_2; $CHCl_3$–EtOH (98 : 2)] to give *ethyl 3-(3-cyclohexyl-3-oxopropyl)-2-[(Z)-6-ethoxycarbonylhex-2-enyl]carbazate* (1.9 g) as a pale yellow oil, R_F 0.5 (SiO_2; $CHCl_3$–EtOH, 98 : 2); $\nu_{max.}$ 3 380, 1 732, and 1 708 cm^{-1}; δ 1.0—2.0 (12 H, m, 6 × CH_2), 1.23 (6 H, t, 2 × OCH_2Me), 2.22 (4 H, m, CH_2CO_2Et and $CH{=}CHCH_2CH_2$), 2.56 (3 H, m, $CH_2COCH<$), 3.08 (2 H, t, $NHCH_2$), 4.07 (6 H, m, $NCH_2CH{=}$ and 2 × OCH_2Me), and 5.49 (2 H, m, $CH{=}CH$). Sodium borohydride reduction of the above ketone in the usual manner afforded *ethyl 3-(3-cyclohexyl-3-hydroxypropyl)-2-[(Z)-6-ethoxycarbonylhex-2-enyl]carbazate* (32) as a colourless oil, R_F 0.4 [SiO_2; $CHCl_3$–EtOH (98 : 2)]; $\nu_{max.}$ 3 450 br, 3 405, 1 734, and 1 700 cm^{-1}; δ 1.0—2.0 (15 H, m, 7 × CH_2 and CH), 1.23 (6 H, t, 2 × OCH_2Me), 2.22 (4 H, m, CH_2CO_2Et and $CH{=}CHCH_2CH_2$), 3.06 and 3.45 (each 1 H, m, non-equiv. $NHCH_2$), 4.07 (7 H, m, $NCH_2CH{=}$, CHOH, and 2 × OCH_2Me), and 5.49 (2 H, m, $CH{=}CH$).

Following the general method of synthesis described above for compound (30a), the carbazate (32) afforded a triazolidinedione ester. The derived carboxylic acid was purified by preparative t.l.c. {R_F 0.5 [SiO_2; $CHCl_3$–MeOH–HOAc (90 : 5 : 5)]} and crystallisation from ethyl acetate–hexane, to give 1-[(Z)-6-*carboxyhex-2-enyl*]-2-(3-*cyclohexyl-3-hydroxypropyl*)-1,2,4-*triazolidine-3,5-dione* (33) as a colourless solid, no sharp m.p. (Found: C, 59.1; H, 7.75; N, 11.2. $C_{18}H_{29}N_3O_5$ requires C, 58.85; H, 7.95; N, 11.45%); $\nu_{max.}$ 3 410 br, 1 712, and 1 570 cm^{-1}; δ ([$^2H_6$]DMSO, 100 °C) 1.0—2.0 (15 H, m, 7 × CH_2 and CH), 2.17 (4 H, m, CH_2CO_2H and $CH{=}CHCH_2CH_2$), 3.39 (3 H, m, NCH_2CH_2 and CHOH), 4.03 (2 H, br, t, $NCH_2CH{=}$), and 5.47 (2 H, m, $CH{=}CH$).

3-(6-*Ethoxycarbonylhexyl*)-4-*octyl*-1,3,4-*oxadiazolidine*-2,5-*dione* (35).—The carbazate (23a) (2.33 g, 6.3 mmol) in dry toluene (38 ml) was added during 15 min to a stirred solution of phosgene in toluene (26 ml, 12.5% w/w) at 5 °C. The solution was stirred for 18 h at room temperature and the solvent was removed *in vacuo*; the residual gum was heated at 175—180 °C under nitrogen for 20 min and the resulting brown glass was purified by column chromatography [SiO_2; Et_2O–hexane (3 : 2)] to give the *ester* (35) (2.1 g, 90%) as a colourless syrup; $\nu_{max.}$ 1 838, 1 764, and 1 732 cm^{-1}; δ 0.88 (3 H, t, Me), 1.25 (3 H, t, OCH_2Me), 1.2—1.8 (20 H, m, 10 × CH_2), 2.33 (2 H, t, CH_2CO_2Et), 3.58 (4 H, t, 2 × NCH_2), and 4.18 (2 H, q, OCH_2Me).

A solution of the ester (35) (185 mg, 0.5 mmol) in ethanol (5 ml) and 1N-aqueous sodium hydroxide (1 ml) was set aside at 5 °C for 2.5 h and then diluted with water. 2N-Hydrochloric acid was added to pH 7, the product was extracted into chloroform, and the extract was dried and evaporated to leave a colourless syrup (190 mg) whose ^1H n.m.r. spectrum was indistinguishable from that of the carbazate (23a).

3-(6-*Carboxyhexyl*)-4-*octyl*-1,3,4-*oxadiazolidine*-2,5-*dione* (37).—A solution of the oxadiazolidinedione ester (35) (470 mg, 1.27 mmol) and iodotrimethylsilane (340 mg, 1.7 mmol) in carbon tetrachloride (10 ml) was refluxed under dry nitrogen for 48 h. The cooled solution was stirred with water (50 ml) for 5 min, the organic phase was washed with aqueous sodium thiosulphate and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Crystallisation of the residual solid from ether–hexane gave the *carboxylic acid* (37) (360 mg, 83%) as cream-coloured needles, m.p. 61—62 °C (Found: C, 63.6; H, 9.65; N, 8.25. $C_{18}H_{32}N_2O_4$ requires C, 63.55; H, 9.4; N, 8.25%); $\nu_{max.}$ (KBr) 1 833, 1 756, and 1 695 cm^{-1}; δ 0.88 (3 H, t, Me), 1.2—1.8 (20 H, m, 10 × CH_2), 2.34 (2 H, t, CH_2CO_2H), 3.56 (4 H, t, 2 × NCH_2), and 8.0 (1 H, br, CO_2H).

A dilute solution of the acid (37) in saturated aqueous sodium hydrogencarbonate (pH *ca.* 9.5) was set aside at room temperature for 2 h. The pH was brought to 7 with 1N-hydrochloric acid and the product was extracted into chloroform; t.l.c. [SiO_2; Et_2O–MeOH (20 : 1)] of the extract showed components of R_F 0.95, 0.40, 0.30, 0.27, and 0.0, in addition to some starting acid, R_F 0.45.

3-*Benzyl*-4-(6-*ethoxycarbonylhexyl*)-1,3,4-*oxadiazolidine*-2,5-*dione*.—The benzylidenecarbazate (21) was converted into the corresponding benzylcarbazate by shaking with 10% palladium–charcoal in ethanol under hydrogen until *ca.* 1 mol equiv. of hydrogen had been absorbed. Reaction with phosgene, followed by pyrolysis, as described above for compound (23a), then gave 3-*benzyl*-4-(6-*ethoxycarbonylhexyl*)1,3,4-*oxadiazolidine*-2,5-*dione* as a colourless gum; δ 1.35 (3 H, t, OCH_2Me), 1.1—1.8 (8 H, m, 4 × CH_2), 2.26 (2 H, t, CH_2CO_2Et), 3.48 (2 H, t, NCH_2CH_2), 4.14 (2 H, q, OCH_2Me), 4.74 (2 H, s, NCH_2Ph), and 7.37 (5 H, s, Ph).

When this gum (350 mg), stirred in ethanol (15 ml) at 5 °C, was treated with sodium borohydride (70 mg), vigorous effervescence ensued. After 30 min, work-up afforded a crude product which was purified by preparative t.l.c. (SiO_2; Et_2O), to give a colourless glass (70 mg); δ 8.02, 8.10, 8.20, and 8.35 (each s, 4 × NCHO), 4.45 and 4.70 (each s, NCH_2Ph; ratio 5 : 12). The data are consistent with a mixture of the *syn* and *anti* forms of 1-benzyl-2-(6-ethoxycarbonylhexyl)-2-formylhydrazine and of 1-benzyl-2-(6-ethoxycarbonylhexyl)-1-formylhydrazine.

3-(6-*Carboxyhexyl*)-4-(3-*cyclohexyl*-3-*hydroxypropyl*)-1,3,4-*thiadiazolidine*-2,5-*dione* (40b).—After alkylation of 1,3,4-thiadiazolidine-2,5-dione (38) [10,13] with t-butyl 7-bromoheptanoate and work-up according to the Du Pont procedure,[10] the product derived from the acidic fraction was subjected to column chromatography [SiO_2; $CHCl_3$–MeOH (9 : 1)] to give pure 3-(6-t-butyloxycarbonylhexyl)-1,3,4-thiadiazolidine-2,5-dione (39). A solution of (39) (1.3 g, 4.3 mmol), 1-cyclohexylprop-2-en-1-one (0.6 g, 4.3 mmol), and benzyltrimethylammonium hydroxide (40% solution in MeOH, 2 drops) in dry dioxan (20 ml) was heated under reflux, monitoring the formation of the less-polar adduct, R_F 0.6 [SiO_2; $CHCl_3$–EtOH (98 : 2)], by t.l.c. After 4 h, the reaction solution was cooled, acidified with a few drops of acetic acid, diluted with ethanol (25 ml), and cooled to 0 °C. Sodium borohydride (150 mg, 4 mmol) was added, the reaction mixture was stirred at room temperature for 5 h, and the solvent was removed *in vacuo*. A suspension of the residue in water was acidified with 0.1N-hydrochloric acid and the oil was extracted into ethyl acetate; the extract was twice washed with 5% aqueous sodium hydrogencarbonate, dried (Na_2SO_4), and evaporated. Purification of the residual yellow oil by column chromatography [SiO_2; $CHCl_3$–EtOH (98 : 2)] gave 3-(6-*t*-*butyloxycarbonylhexyl*)-4-(3-*cyclohexyl*-3-*hydroxypropyl*)-1,3,4-*thiadiazolidine*-2,5-*dione* (40a) as a colourless oil (1.0 g), *m/e* 442 (M^+, $C_{22}H_{38}N_2O_5S$); $\nu_{max.}$ 3 450 (OH), 1 733 (ester), and 1 695 and 1 680 cm^{-1} (ring carbonyls); δ 1.0—2.0 (21 H, m, 10 × CH_2 and CH), 1.40 (9 H, s, $OCMe_3$), 2.28 (2 H, t, $CH_2CO_2CMe_3$), and 3.58 (5 H, m, 2 × NCH_2 and $CHOH$).

A solution of the ester (40a) (950 mg) in cold trifluoroacetic acid (10 ml) was set aside at 0 °C for 1.5 h and then concentrated *in vacuo* at 0 °C. Benzene (40 ml) was added, the solution was evaporated *in vacuo* at room temperature, and the residual oil was stirred with 5% aqueous sodium hydrogencarbonate (50 ml) for 1 h. Undissolved material was removed with ether, the clear aqueous solution was acidified with 0.1N-hydrochloric acid, and the liberated carboxylic acid was extracted into ether. The ethereal solution was dried (Na_2SO_4) and evaporated, and the residue was purified by preparative t.l.c. {R_F 0.3 [SiO_2; $CHCl_3$–MeOH (19 : 1)]}, to give the *carboxylic acid* (40b) as a colourless gum (600 mg); $\nu_{max.}$ 3 400 br (OH), 1 720sh (CO_2H), and 1 670br cm^{-1} (ring carbonyls).

We are indebted to Mrs. J. P. North and Messrs. P. Boehm, A. C. Capocci, C. J. Dalton, P. Lowing and R. J. Stepney for invaluable technical assistance. We also thank Dr. B. J. R. Whittle and Mr. S. Bunting for the biological data, and Dr. A. J. Everett and his staff for the spectroscopic, pK_a, and microanalytical data.

[0/1981 *Received*, 30*th December*, 1980]

REFERENCES

[1] Part 3, M. A. Brockwell, A. G. Caldwell, N. Whittaker, and M. J. Begley, *J. Chem. Soc., Perkin Trans. 1*, 1981, 706.
[2] C. J. Harris, N. Whittaker, G. A. Higgs, J. M. Armstrong, and P. M. Reed, *Prostaglandins*, 1978, **16**, 773.
[3] (*a*) A. G. Caldwell, C. J. Harris, R. Stepney and N. Whittaker, *J. Chem. Soc., Chem. Commun.*, 1979, 561; (b) *J. Chem. Soc., Perkin Trans. 1*, 1980, 495.
[4] A. Novacek and J. Gut, *Coll. Czech. Chem. Commun.*, 1967, **32**, 190.
[5] A. M. Khaletskii and B. L. Moldaver, *Russ. Chem. Rev.* (*Engl. Transl.*), 1963, **32**, 535; G. Hallman, I. Ringhardtz, and U. Fischer, *Chem. Ber.*, 1957, **90**, 537.
[6] W. H. Pirkle and P. L. Gravel, *J. Org. Chem.*, 1978, **43**, 808.
[7] D. R. Adams, A. F. Barnes and F. Cassidy, *Tetrahedron Lett.*, 1979, 3335.
[8] C. D. Hurd and F. F. Cesark, *J. Am. Chem. Soc.*, 1967, **89**, 1417.
[9] M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, 1977, **99**, 968; T-L. Ho and G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 774.
[10] U.S. Patent 4,032,533, Du Pont, 1977 (*Chem Abs.*, 1977 **87**, 151763y).
[11] A. Einhorn and R. Feibelmann, *Liebigs Ann. Chem.*, 1908, **359**, 186.
[12] J. Thiele and A. Lachman, *Liebigs Ann. Chem.*, 1895, **288**, 293.
[13] K. Rüfenacht, *Helv. Chim. Acta*, 1968, **51**, 518.