The Synthesis of 8,10,12-Triazaprostaglandin Analogues: 1,2,4-Triazolidine-3,5-dione Derivatives

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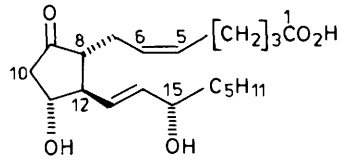
In the search for active, more selective prostaglandin analogues, the synthesis of 8,10,12-triazaprostaglandin analogues† has been achieved from readily available 4-methyl-1,2,4-triazolidine-3,5-dione. The general approach involved introduction of the α- and ω-side-chain as entire units by step-wise *N*-alkylation. The problems encountered with this approach of competing *N*-and *O*-mono- and di-alkylation were overcome, eventually, such that judicious choice of the initial mono-*N*-alkylation step enabled the synthesis of analogues incorporating wide variations in the α- and ω-side-chain. Important structural modifications included introduction of unsaturation into the α-side-chain at the 5,6-position and of methyl groups into the ω-side-chain at the 15- and 16-position as exemplified by the synthesis of 1-[(*Z*)-6-carboxyhex-2-enyl]-2-(3-hydroxy-3,4-dimethyloctyl)-4-methyl-1,2,4-triazolidine-3,5-dione (**19**). The stable triazaprostaglandin analogues were synthesized as racemic compounds but, nevertheless, compound (**19**) possessed bronchodilator activity of a similar order to that of the natural prostaglandins PGE_1 and PGE_2.

The apparent role of prostaglandins in many physiological processes has led to a search for compounds that either mimic or selectively antagonize natural prostaglandins for use as potential therapeutic agents.[1,2] The major objective has been to obtain compounds with a more selective pharmacological action and, consequently, a better therapeutic ratio than natural prostaglandins such as PGE_2. In the search for such compounds

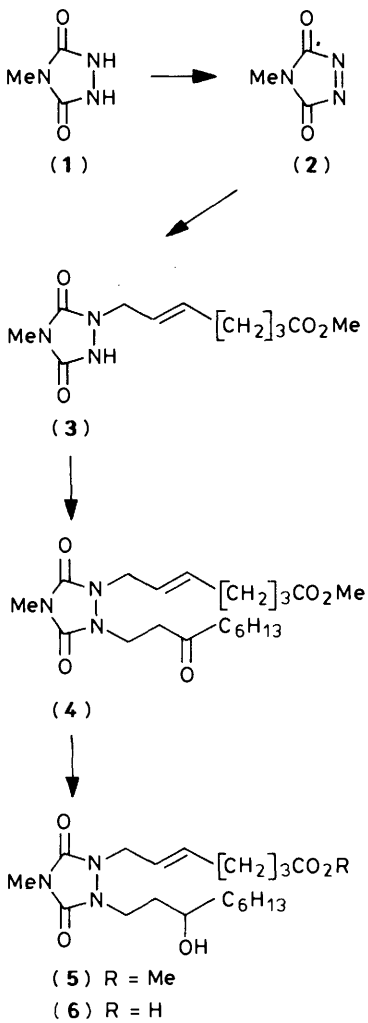


Prostaglandin E_2

synthetic routes to azaprostaglandin analogues have been developed in our laboratories, and it was found that 12-aza-[3] and 10,12-diaza-prostaglandin analogues[4,†] retained much of the biological activity exhibited by the natural prostaglandins, a finding confirmed by other groups.[5–7] In earlier reports[8,9] our interest in 8,10,12-triazaprostaglandin analogues was disclosed and routes to some types of analogue were outlined. The triaza series was of particular interest because the compounds potentially were easier to synthesize, and contained fewer asymmetric centres than either natural prostaglandins or 12-aza- and 10,12-diaza-analogues. In this paper we report versatile procedures for the synthesis of a variety of 8,10,12-triazaprostaglandin analogues from readily available 4-substituted 1,2,4-triazolidine-3,5-diones, such as 4-methylurazole.[10]

Results and Discussion

In principle the symmetry of 4-methylurazole (**1**) (Scheme 1) allows the alkylation steps that are necessary to introduce the α- and ω-side-chains to be carried out in any sequence. However, for this approach to be successful it is essential that only mono-*N*-alkylation is obtained in the initial alkylation step. The problem of obtaining regioselective monoalkylation can be



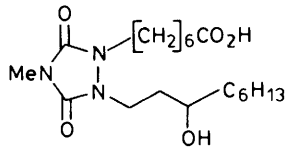
Scheme 1.

† Prostanoic acid numbering.

demonstrated by our initial attempts to introduce the carboxylic acid-containing α-side-chain by alkylation of (**1**) with either saturated or unsaturated ω-bromo esters. Only very low yields of monoalkylated product were obtained, the major products being *O*- and *N*-dialkylated material together with unchanged starting material. Other workers have experienced similar problems in synthesizing 8,12-diazaprostaglandin analogues from 4,4-diethylpyrazolidine-3,5-dione.[11] However, in our series regiospecific introduction of an α-side-chain was achieved initially by using an ene reaction[12,13] (see Scheme 1).

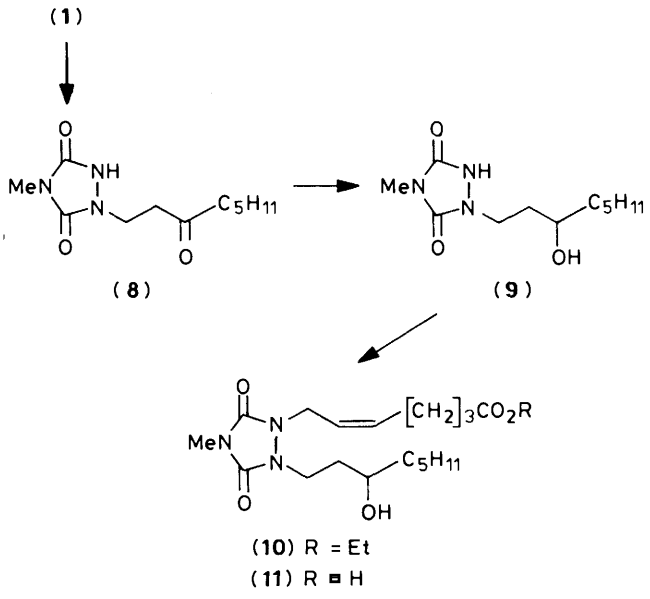
Oxidation of the triazolidinedione (**1**)[10] with dinitrogen tetraoxide[14] in dichloromethane yielded the 3*H*-triazoledione (**2**) which was used without further purification in an ene reaction with hept-6-enoic acid[15] in refluxing benzene. The resulting crude acid was esterified and the unsaturated methyl ester (**3**) was isolated as a crystalline solid after column chromatography in an overall yield of 37% from (**1**). The *E* stereochemistry of the double bond in (**3**) was verified by ^{1}H n.m.r. decoupling experiments. Irradiation of the signal at δ 4.05 (2 H, m, $NCH_2CH{=}CH$) caused the sextuplet at δ 5.48 (1 H) to collapse to a doublet of coupling constant *J* 15 Hz. Irradiation at δ 2.09 (presumably $NCH_2CH{=}CHCH_2$) caused the signal at δ 5.80 (1 H, m) to collapse to a doublet with *J* 15 Hz, thus confirming the *E* stereochemistry. Stork and Kraus[16] have reported an (*E*)-orientated product from a thermal ene reaction. Introduction of the ω-side-chain was achieved readily by Michael addition of the unsaturated ester (**3**) to non-1-en-3-one in dioxane in the presence of benzyltrimethylammonium hydroxide to afford (**4**). Reduction of (**4**) with sodium borohydride and isolation of the product by column chromatography gave the triazaprostaglandin analogue (**5**) as a gum in 75% overall yield from (**3**). Alkaline hydrolysis of the ester (**5**) gave the desired carboxylic acid (**6**) as a viscous gum.

The biological activity of the acid (**6**) was disappointing, it being about 250 times less active as a bronchodilator[9] than PGE_1 or PGE_2. The lower activity might have been a reflection of the *E* stereochemistry of the 5,6-double bond which is not a feature of natural prostaglandins. Consequently this prompted the synthesis of analogues in which the α-side-chain was either fully saturated or contained a (*Z*)-5,6-double bond to give analogues with α-side-chains identical with those found in PGE_1 or PGE_2, respectively. The saturated analogue (**7**) was obtained by hydrogenation of the unsaturated ester (**3**) over palladium–charcoal and transformation of the resulting compound (**12**) (see Scheme 3) by the methods described for Scheme 1. Compound (**7**) proved to be about 7 times more active[9] than (**6**).



(**7**)

In order to prepare analogues with *Z* stereochemistry about the 5,6-double bond it was necessary to introduce the ω-side-chain first (see Scheme 2). Attempts to monoalkylate 4-methylurazole with ethyl (*Z*)-7-bromohept-5-enoate[17] resulted mainly in dialkylation. However, initial mono-*N*-alkylation was achieved by Michael addition of 4-methylurazole to oct-1-en-3-one to give the ketone (**8**), which was isolated as a crystalline solid in 71% yield. Borohydride reduction of (**8**) and alkylation of the resulting alcohol (**9**) with ethyl (*Z*)-7-bromohept-5-enoate in dry dimethylformamide (DMF) using anhydrous lithium carbonate as base gave the prostaglandin triaza analogue (**10**) in high yield. Chromatographic purification of



(**10**) R = Et
(**11**) R = H

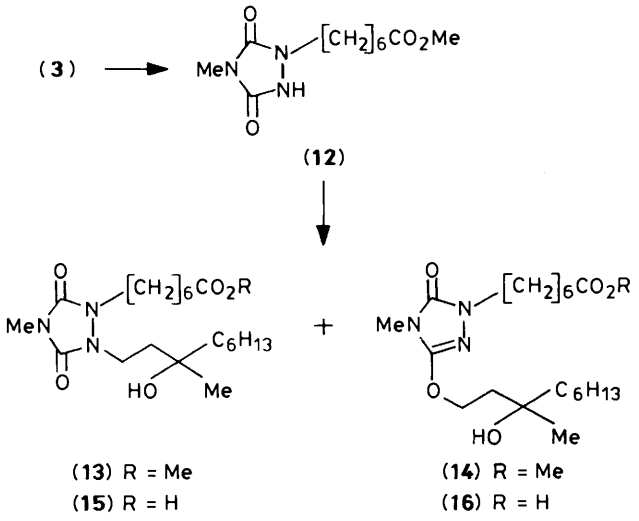
Scheme 2.

the ester (**10**) and subsequent alkaline hydrolysis gave the desired carboxylic acid (**11**) as a viscous gum in 45% overall yield from (**1**). The olefinic coupling constant in compound (**10**), which possesses *Z* stereochemistry about the 5,6-double bond, was found to be 12.5 Hz compared with that of 15 Hz found in the (*E*)-compound (**3**). Introduction of a (*Z*)-5,6-double bond into the α-side-chain of these analogues increased bronchodilator activity about 5 times compared with the corresponding (*E*)-5,6 analogues,[9,18] and the activity of the (*Z*)-compounds was, therefore, similar to that of the saturated compounds.

It is known that natural prostaglandins are inactivated rapidly in the body by the 15-hydroxydehydrogenase enzyme which oxidises the important secondary hydroxy group at C-15 to a ketone.[19] It was assumed that this would occur with 8,10,12-triazaprostaglandin analogues such as (**6**), (**7**), and (**11**), and indeed such compounds, whilst possessing short lived bronchodilator activity when given intravenously, were inactive when given orally. This problem of rapid metabolic inactivation has been partially overcome in natural prostaglandins by introduction of a 15-methyl group, thus preventing oxidation.[20,21] It appeared to be a relatively simple task to introduce a 15-methyl group into our compounds by treatment of compounds such as (**8**) or (**4**) with methylmagnesium iodide or methyl-lithium. However, this simple, direct approach was unsuccessful since the 15-ketone group in these analogues was remarkably resistant to attack by such carbon nucleophiles. Nevertheless, certain of the required 15-methyl compounds were obtained by an alternative approach (see Scheme 3).

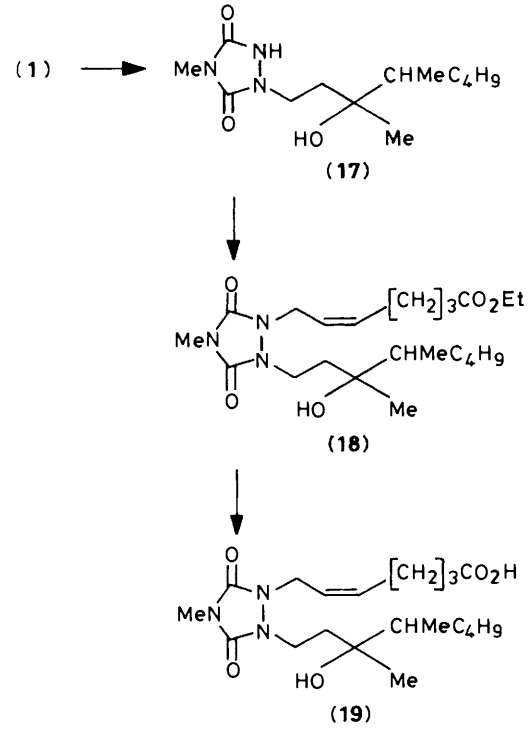
Alkylation of (**12**) with 3-methyl-1-(*p*-tolylsulphonyloxy)-nonan-3-ol in hexamethylphosphoramide (HMPA) in the presence of sodium iodide and sodium carbonate gave a mixture of the *N*-alkylated product (**13**) together with the *O*-alkylated product (**14**) in the ratio 3:1. Careful chromatography on silica gave the triaza analogue (**13**) in yields of about 30%. Hydrolysis of the methyl ester group gave the required carboxylic acid (**15**), which was isolated as a crystalline solid. The corresponding *O*-alkylated compound (**16**) was also prepared from its methyl ester (**14**), but it proved to be biologically inactive.

Although the approach shown in Scheme 3 was not particularly satisfactory, competing *N*- and *O*-alkylation caused even greater problems when we attempted to synthesize



Scheme 3.

analogues incorporating both a (*Z*)-5,6-double bond in the α-side-chain and a 15-methyl group in the ω-side-chain. If initial alkylation were attempted with the α-side-chain, predominantly dialkylation occurred, whereas if initial alkylation were attempted with the ω-side-chain using a tosylate, then a complex mixture of *N*- and *O*-mono- and di-alkylated products was obtained. This problem was solved eventually by using alkyl bromides rather than tosylates as alkylating agents (see Scheme 4).



Scheme 4.

Thus alkylation of 4-methylurazole with 1-bromo-3,4-dimethyloctan-3-ol in dimethyl sulphoxide (DMSO) in the presence of 5 equivalents of sodium hydrogen carbonate gave a 77% yield of the mono-*N*-alkylated compound (**17**), with little or no evidence of any *O*-alkylated compounds being formed. Further alkylation of (**17**) with ethyl (*Z*)-7-bromohept-5-enoate, followed by alkaline hydrolysis of the ethyl ester (**18**), afforded the carboxylic acid (**19**) as a viscous gum. It had been shown in previous studies that the presence of both a 15- and a 16-methyl group in the ω-side-chain tended to yield optimum biological activity.[9]

Thus, by judicious choice of the initial regioselective monoalkylation step, procedures have been developed that enable the synthesis of 8,10,12-triazaprostaglandin analogues incorporating wide variations in the α- and ω-side-chain to be carried out. Although the analogues were isolated as racemic mixtures, h.p.l.c. with reverse-phase conditions indicated that separation of the 15,16-dimethyl analogues (**18**) and (**19**) into, presumably, two racemic diastereoisomers was possible, but no attempt was made to separate the isomers on a preparative scale. By using the approaches described in this paper, analogues with potent, long acting oral bronchodilator activity have been obtained.[18]

Experimental

T.l.c. was performed on Eastman Kodak silica gel 13181 plates and compounds were rendered visible by iodine vapour and cerium(IV) ammonium nitrate spray. Column chromatography was carried out with Merck Kieselgel 60 (70—230 mesh). I.r. spectra were recorded, with a Perkin-Elmer 197 spectrophotometer, as neat films or Nujol mulls. ^{1}H N.m.r. spectra were determined for solutions in deuteriochloroform or [$^2H_6$]DMSO using a Perkin-Elmer R 12A (60 MHz), Varian EM 360A (60 MHz), Varian CFT 20A (80 MHz), or Perkin-Elmer R 32 (90 MHz) spectrometer with tetramethylsilane as internal standard; in the spectra, sx means sextet. Mass spectra (e.i. and c.i.) were obtained on a VG 7070F spectrometer at 70 eV, and c.i. mass spectra were obtained using ammonia as reagent gas. Solutions were dried over anhydrous sodium sulphate and solvents were evaporated under reduced pressure using a rotary film evaporator. Accurate elemental analyses were difficult to obtain for many of the viscous gums since they retained solvents tenaciously.

1-[(E)-6-*Methoxycarbonylhex*-2-*enyl*]-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**3**).—A stirred suspension of 4-methyl-1,2,4-triazolidine-3,5-dione (**1**) (23 g, 0.2 mol) in dichloromethane (250 ml) was cooled to −5 °C. Dinitrogen tetraoxide (24 ml) in dichloromethane (100 ml) was added dropwise, and the mixture was stirred until a clear, deep red solution was obtained. Sodium sulphate (20 g) was added and the reaction mixture was stirred for 20 min and then filtered. The filtrate was evaporated under reduced pressure to give 4-methyl-4,5-dihydro-3*H*-1,2,4-triazole-3,5-dione (**2**) as red needles (22 g), m.p. 105 °C (decomp.).

To a solution of the dione (**2**) (22 g) in benzene (200 ml) was added a solution of hept-6-enoic acid[15] (23 g, 0.18 mol) in benzene (100 ml) and the mixture was heated under reflux for 1 h. Evaporation under reduced pressure gave an oil which was treated with 10% acetyl chloride in dry methanol (300 ml) and the solution was heated under reflux for 5 h. Evaporation under reduced pressure gave an oil which was chromatographed on Kieselgel 60 (900 g) with chloroform–methanol (19:1) as eluant. Combination of the appropriate fractions gave 1-[(*E*)-6-methoxycarbonylhex-2-enyl]-4-methyl-1,2,4-triazolidine-3,5-dione (19 g, 37%), m.p. 55—57 °C (from $CHCl_3$) (Found: C, 51.55; H, 6.6; N, 16.6. Calc. for $C_{11}H_{17}N_3O_4$: C, 51.8; H, 6.7; N, 16.5%); $\nu_{max.}$(melt) 1 760 (NCO), 1 740 (ester), and 1 670 cm^{-1} (NCO); δ_H (90 MHz; $CDCl_3$) 3.05 (3 H, s, NCH_3), 3.66 (3 H, s, CO_2CH_3), 4.05 (2 H, br d, NCH_2), 5.48 (1 H, ăx, $J_{5,6}$ 15, $J_{6,7}$ 6 Hz, NCH_2CH=CH), 5.80 (1 H, sx, $J_{5,6}$ 15, $J_{4,5}$ 6 Hz, NCH_2CH=C*H*), and 8.00—8.95 (1 H, br s, NH); *m/z* 255 (M^+, 1%), 224 (2), 141 (33), and 81 (100).

1-(3-*Hydroxynonyl*)-2-[(E)-6-*methoxycarbonylhex*-2-*enyl*]-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**5**).—A solution of 1-[(*E*)-6-methoxycarbonylhex-2-enyl]-4-methyl-1,2,4-triazolidine-3,5-dione (2.8 g, 10.9 mmol) in dioxane (20 ml) was treated with non-1-en-3-one (see below) (1.84 g, 13.1 mmol) and methanolic benzyltrimethylammonium hydroxide (3 drops; 40% solution). The mixture was heated under reflux for 3 h, and then evaporated to dryness. Chromatography of the residual oil on Kieselgel 60 (120 g) with chloroform as eluant gave 1-[(*E*)-6-methoxycarbonylhex-2-enyl]-4-methyl-2-(3-oxononyl)-1,2,4-triazolidine-3,5-dione (**4**) as an oil (3.62 g, 83%).

A solution of the foregoing ketone (3.62 g, 9.17 mmol) in dry methanol (40 ml) was treated with sodium borohydride (0.38 g, 11.18 mmol), and the solution was stirred at 25 °C for 2 h. The excess of borohydride was decomposed with glacial acetic acid, and the mixture was partitioned between ether (250 ml) and water (250 ml). Evaporation of the organic layer under reduced pressure gave an oil (3.44 g) which was chromatographed on Kieselgel 60 (100 g) with chloroform as eluant. Combination of the appropriate fractions gave 1-(3-*hydroxynonyl*)-2-[(E)-6-*methoxycarbonylhex*-2-*enyl*]-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**5**) as a gum (3.30 g, 90%) (Found: M^+, 397.2582. $C_{20}H_{35}N_3O_5$ requires M, 397.2573); $\nu_{max.}$(film) 3 460 (OH), 1 765 (NCO), 1 735 (ester), and 1 700 cm^{-1} (NCO); δ_H (60 MHz; $CDCl_3$) 0.87 (3 H, br t, CH_3), 1.10—2.50 (18 H, m, chains), 3.05 (3 H, s, NCH_3), 3.67 (3 H, s, CO_2CH_3), 3.50—3.95 (3 H, m, NCH_2 and C*H*OH), 4.15 (2 H, t, NCH_2CH=CH), and 5.10—5.90 (2 H, m, olefinic); *m*/*z* 397 (M^+, 8%), 366 (5), 312 (2), and 141 (100).

1-[(E)-6-*Carboxyhex*-2-*enyl*]-2-(3-*hydroxynonyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**6**).—The following method, described for the carboxylic acid (**6**), was employed for the hydrolysis of all esters. A solution of 1-(3-hydroxynonyl)-2-[(*E*)-6-methoxycarbonylhex-2-enyl]-4-methyl-1,2,4-triazolidine-3,5-dione (**5**) (3.32 g, 8.36 mmol) in methanol (80 ml) and 10% aqueous sodium carbonate (25 ml) was stirred and heated under reflux for 15 h. The reaction mixture was poured into water (250 ml) and extracted with ether (250 ml), and the extract was discarded. The aqueous layer was adjusted to pH 2 and extracted with ether (3 × 100 ml). Evaporation of the combined extracts gave 1-[(*E*)-6-carboxyhex-2-enyl]-2-(3-hydroxynonyl)-4-methyl-1,2,4-triazolidine-3,5-dione (**6**) as a pale yellow gum (2.8 g, 89%)[8] (Found: C, 59.0; H, 8.7; N, 10.7%; M^+, 383.2427. Calc. for $C_{19}H_{33}N_3O_5$: C, 59.5; H, 8.7; N, 11.0%; M, 383.2418); $\nu_{max.}$(film) 3 650—2 400 (OH), 1 765 (NCO), and 1 710—1 620 cm^{-1} (NCO and CO_2H); δ_H (60 MHz; $CDCl_3$) 0.60—2.50 (21 H, m, chains), 3.04 (3 H, s, NCH_3), 3.20—3.95 (3 H, m, NCH_2 and C*H*OH), 4.05 (2 H, d, NCH_2CH=CH), and 4.90—6.00 [4 H, m, CH=CH, and 2 × OH (exchanged with D_2O)]; *m*/*z* 383 (M^+, 2%), 298 (1), 127 (41), and 69 (100).

1-(6-*Carboxyhexyl*)-2-(3-*hydroxynonyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**7**).—This compound was obtained as a viscous gum in 89% yield by hydrolysis of its ester using the method described for the preparation of compound (**6**) (Found: C, 58.7; H, 9.4; N, 10.4%; M^+, 385.2558. $C_{19}H_{35}N_3O_5$ requires C, 59.2; H, 9.15; N, 10.9%; M, 385.2577); $\nu_{max.}$(film) 3 600—2 500 (OH), 1 770 (NCO), and 1 700 cm^{-1} (CO_2H); δ_H (60 MHz; $CDCl_3$) 0.88 (3 H, br t, CH_3), 1.08—2.00 (20 H, m, chains), 2.32 (2 H, t, CH_2CO_2H), 2.97 (3 H, s, NCH_3), 3.30—4.01 (5 H, m, 2 × NCH_2 and C*H*OH), and 6.50 (2 H, br s, 2 × OH, exchanged with D_2O); *m*/*z* 385 (M^+, 0.4%), 300 (1), 225 (10), and 128 (100).

4-*Methyl*-1-(3-*oxo-octyl*)-1,2,4-*triazolidine*-3,5-*dione* (**8**).—A solution of 4-methyl-1,2,4-triazolidine-3,5-dione (15 g, 0.13 mol) and oct-1-en-3-one (see below) (14.8 g, 0.12 mol) in dioxane (200 ml) was treated with 40% methanolic benzyltrimethylammonium hydroxide (15 drops) and heated under reflux for 24 h. The mixture was allowed to cool, poured into water (300 ml), and extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with brine (2 × 100 ml) and dried. Evaporation under reduced pressure gave a white solid which on recrystallization from ethyl acetate–n-hexane gave 4-*methyl*-1-(3-*oxo-octyl*)-1,2,4-*triazolidine*-3,5-*dione* (**8**) (20.1 g, 71%), m.p. 75—77 °C (Found: C, 55.1; H, 8.3; N, 17.5. $C_{11}H_{19}N_3O_3$ requires C, 54.8; H, 7.9; N, 17.4%); $\nu_{max.}$(Nujol) 1 760 (NCO), 1 740 (CO), and 1 700 cm^{-1} (NCO); δ_H (60 MHz; [$^2H_6$]DMSO) 0.80—1.80 (9 H, m, chain), 2.20—2.85 (4 H, m, CH_2COCH_2), 2.90 (3 H, s, NCH_3), and 3.65 (2 H, t, NCH_2); *m*/*z* 241 (M^+, 20%), 127 (100), 115 (45), and 83 (35).

1-(3-*Hydroxyoctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**9**).—A solution of 4-methyl-1-(3-oxo-octyl)-1,2,4-triazolidine-3,5-dione (**8**) (11.51 g, 48 mmol) in ethanol (100 ml) was stirred at 20 °C, and sodium borohydride (2 g, 53 mmol) was added in portions during 4 h. After the mixture had been stirred for a further 1 h, the excess of borohydride was decomposed with acetic acid and the mixture was evaporated to dryness. The residue was partitioned between ethyl acetate (250 ml) and 1M hydrochloric acid (250 ml), and the aqueous layer was extracted further with ethyl acetate (2 × 100 ml). The combined organic layers were washed with brine (250 ml) and dried. Evaporation under reduced pressure gave an oil which solidified to give 1-(3-*hydroxyoctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**9**) as a waxy solid (10.5 g, 91%), m.p. 82—84 °C (from ethyl acetate) (Found: C, 54.7; H, 9.0; N, 16.7%; M^+, 243.1577. $C_{11}H_{21}N_3O_3$ requires C, 54.3; H, 8.7; N, 17.3%; M, 243.1582); $\nu_{max.}$(Nujol) 3 500 (OH), 1 755 (NCO), and 1 695 cm^{-1} (NCO); δ_H (60 MHz; [$^2H_6$]DMSO) 0.87 (3 H, br t, CH_3), 1.10—1.80 (10 H, m, 5 × CH_2), 2.87 (3 H, s, NCH_3), and 3.20—3.75 (4 H, m, NCH_2 and CHOH); *m*/*z* 243 (M^+, 20%), 225 (27), 168 (70), 128 (100), and 115 (60).

1-[(Z)-6-*Ethoxycarbonylhex*-2-*enyl*]-2-(3-*hydroxyoctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**10**).—A solution of 1-(3-hydroxyoctyl)-4-methyl-1,2,4-triazolidine-3,5-dione (**9**) (4.47 g, 18.55 mmol) in dry DMF (50 ml) was stirred at room temperature and ethyl (*Z*)-7-bromohept-5-enoate[17] (see below) (4.40 g, 18.72 mmol) and anhydrous lithium carbonate (3.00 g, 44.8 mmol) were added. After 2 days the resultant suspension was partitioned between ethyl acetate (250 ml) and water (250 ml), and acidified with 3M hydrochloric acid. The organic layer was washed in turn with water (2 × 100 ml) and brine (100 ml), and dried. Evaporation under reduced pressure gave an oil (7.8 g) which was chromatographed on Kieselgel 60 (80 g) with n-hexane–ethyl acetate (3:2) as eluant. Combination of the appropriate fractions gave 1-[(Z)-6-*ethoxycarbonylhex*-2-*enyl*]-2-(3-*hydroxyoctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**10**) as an oil (5.93 g, 81%) (Found: C, 60.0; H, 8.9; N, 10.6. $C_{20}H_{35}N_3O_5$ requires C, 60.4; H, 8.9; N, 10.6%); $\nu_{max.}$(film) 3 460 (OH), 1 770 (NCO), 1 735 (ester), and 1 705 cm^{-1} (NCO); δ_H (80 MHz; $CDCl_3$) 0.90 (3 H, br t, CH_3), 1.28 (3 H, t, $CO_2CH_2CH_3$), 1.10—1.95 (12 H, m, chains), 2.00—2.50 (4 H, m, CH_2CO_2Et and CH=CHCH_2), 2.55 (1 H, s, OH, exchanged with D_2O), 3.08 (3 H, s, NCH_3), 3.30—3.90 (3 H, m, NCH_2 and C*H*OH), 3.95—4.35 (4 H, NCH_2CH=CH and $CO_2CH_2CH_3$), and 5.15—5.85 (2 H, m, CH=CH); *m*/*z* 397 (M^+, 3%), 379 (2), 326 (10), and 155 (100).

1-[(Z)-6-*Carboxyhex*-2-*enyl*]-2-(3-*hydroxyoctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**11**).—This compound was obtained as a viscous gum in 97% yield by hydrolysis of ester (**10**) using the method described for the preparation of compound (**6**) (Found: C, 58.4; H, 8.6; N, 11.1. $C_{18}H_{31}N_3O_5$ requires C, 58.2;

H, 8.5; N, 11.4%); $\nu_{max.}$(film) 3 650—2 300 (OH) and 1 800—1 600 cm^{-1} (NCO and CO_2H); δ_H (80 MHz; $CDCl_3$) 0.75—1.95 (15 H, m, chains), 2.00—2.50 (4 H, m, CH=CHCH_2 and CH_2CO_2H), 3.07 (3 H, s, NCH_3), 3.15—4.00 (3 H, m, NCH_2 and C*H*OH), 4.20 (2 H, d, NCH_2CH=CH), 5.00 (2 H, br s, OH and CO_2H, exchanged with D_2O), and 5.10—5.85 (2 H, m, CH=CH); *m/z* 369 (M^+, 12%), 298 (10), 243 (40), and 127 (100).

1-(6-*Methoxycarbonylhexyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**12**).—A solution of 1-[(*E*)-6-methoxycarbonylhex-2-enyl]-4-methyl-1,2,4-triazolidine-3,5-dione (**3**) (12.4 g, 48.6 mmol) in 1,2-dimethoxyethane (200 ml) was hydrogenated at atmospheric pressure over 10% Pd–C. After uptake of hydrogen (about 1 100 ml) had ceased, the catalyst was removed by filtration through a pad of Kieselguhr. Evaporation of the filtrate under reduced pressure gave 1-(6-*methoxycarbonylhexyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**12**) as a waxy solid (12.3 g, 98%), m.p. 80—81 °C (Found: C, 51.1; H, 7.7; N, 16.4. $C_{11}H_{19}N_3O_4$ requires C, 51.35; H, 7.4; N, 16.3%); $\nu_{max.}$(Nujol) 1 780—1 660 cm^{-1} (NCO, ester); δ_H (60 MHz; $CDCl_3$) 1.22—1.93 (8 H, m, 4 × CH_2), 2.27 (2 H, m, C$H_2CO_2CH_3$), 3.03 (3 H, s, NCH_3), and 3.52 (5 H, m, NCH_2 and CO_2CH_3); *m/z* 257 (M^+, 5%), 226 (15), 128 (100), and 115 (81).

1-(3-*Hydroxy*-3-*methylnonyl*)-2-(6-*methoxycarbonylhexyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**13**).—A solution of 1-(6-methoxycarbonylhexyl)-4-methyl-1,2,4-triazolidine-3,5-dione (**12**) (6.43 g, 25 mmol) and 3-methyl-1-(*p*-tolylsulphonyloxy)-nonan-3-ol (see below) (8.20 g, 25 mmol) in HMPA (70 ml) was treated with sodium iodide (1.0 g, 7 mmol) and sodium carbonate (3.18 g, 30 mmol), and the resultant suspension was stirred at 25 °C for 70 h. The reaction mixture was poured into water (200 ml), acidified with 10% hydrochloric acid, and the product was extracted into ethyl acetate (3 × 200 ml). The combined extracts were washed successively with water (3 × 250 ml) and saturated brine (3 × 250 ml), and dried. Evaporation under reduced pressure gave a gum (9.54 g) which was chromatographed on Kieselgel 60 (500 g) with chloroform–methanol (49:1) as eluant to give two compounds. Combination of the fractions containing the less polar compound gave 1-(3-hydroxy-3-methylnonyl)-2-(6-methoxycarbonylhexyl)-4-methyl-1,2,4-triazolidine-3,5-dione (**13**) as a gum (2.95 g, 29%)[8] (Found: C, 60.5; H, 9.7; N, 10.05%; M^+, 413.2829. Calc. for $C_{21}H_{39}N_3O_5$: C, 61.0; H, 9.5; N, 10.2%; *M*, 413.2769); $\nu_{max.}$(film) 3 500 (OH), 1 770 (NCO), 1 740 (ester), and 1 680 cm^{-1} (NCO); δ_H (60 MHz; $CDCl_3$) 0.70—2.00 (27 H, m, chains), 2.16—2.54 (2 H, m, C$H_2CO_2CH_3$), 3.04 (3 H, s, NCH_3), 3.65 (3 H, s, CO_2CH_3), and 3.20—4.00 (4 H, m, 2 × NCH_2); *m/z* 413 (M^+, 24%), 328 (20), and 128 (100).

3,4-*Dihydro*-5-(3-*hydroxy*-3-*methylnonyloxy*)-2-(6-*methoxycarbonylhexyl*)-4-*methyl*-1,2,4-*triazol*-3(2H)-*one* (**14**).—Combination of the fractions containing the more polar compound gave (**14**) as an oil (1.33 g, 13%), $\nu_{max.}$(film) 3 400 (OH), 1 730 (ester), 1 700 (NCO), and 1 610 cm^{-1} (C=N); δ_H (60 MHz; $CDCl_3$) 0.90 (3 H, br t, CH_3), 1.05—2.15 (23 H, m, chains), 2.31 (2 H, t, C$H_2CO_2CH_3$), 3.11 (3 H, s, NCH_3), 3.59—3.82 (5 H, m, NCH_2 and CO_2CH_3), and 4.45 (2 H, t, OCH_2); *m/z* 413 (M^+, 1%), 328 (10), and 255 (100).

1-(6-*Carboxyhexyl*)-2-(3-*hydroxy*-3-*methylnonyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**15**).—This compound[8] was obtained as a viscous gum, which solidified with time, in 98% yield by hydrolysis of ester (**13**) using the method described for the preparation of compound (**6**). The acid (**15**) was recrystallized from ethyl acetate, m.p. 52—54 °C (Found: C, 59.6; H, 9.6; N, 10.4%; M^+, 399.2688. Calc. for $C_{20}H_{37}N_3O_5$: C, 60.1; H, 9.3; N, 10.5%; *M*, 399.2642); $\nu_{max.}$(Nujol) 3 500—2 500 (OH), 1 770 (NCO), and 1 760—1 660 cm^{-1} (NCO and CO_2H); δ_H (60 MHz; [$^2H_6$]DMSO) 0.88 (3 H, br t, CH_3), 1.07—1.80 (23 H, m, chains), 2.19 (2 H, t, CH_2CO_2H), 2.91 (3 H, s, NCH_3), and 3.30—3.80 (4 H, m, 2 × NCH_2); *m/z* 399 (M^+, 32%), 314 (12), 226 (75), and 128 (100).

2-(6-*Carboxyhexyl*)-3,4-*dihydro*-5-(3-*hydroxy*-3-*methylnonyloxy*)-4-*methyl*-1,2,4-*triazol*-3(2H)-*one* (**16**).—This compound was obtained as a gum in 90% yield by hydrolysis of ester (**14**) using the method described for the preparation of compound (**6**) (Found: C, 59.9; H, 9.4; N, 10.7. $C_{20}H_{37}N_3O_5$ requires C, 60.1; H, 9.3; N, 10.5%); $\nu_{max.}$(film) 3 480 (OH), 1 760 (NCO), 1 710 (CO_2H), and 1 690 cm^{-1} (NCO); *m/z* 399 (M^+, 3%), 314 (12), and 225 (100).

1-(3-*Hydroxy*-3,4-*dimethyloctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**17**).—A solution of 4-methyl-1,2,4-triazolidine-3,5-dione (**1**) (10 g, 87 mmol) and 1-bromo-3,4-dimethyloctan-3-ol (see below) (10 g, 42 mmol) in DMSO (100 ml) was treated with sodium hydrogen carbonate (20 g, 238 mmol), and the resultant suspension was stirred at 20 °C for 3 d. The mixture was diluted with 1% aqueous sodium hydroxide (550 ml) and extracted with ether (200 ml). The aqueous layer was adjusted to pH 2 with conc. hydrochloric acid and then extracted with ethyl acetate (3 × 200 ml). The combined ethyl acetate extracts were washed with brine (100 ml) and evaporated to give 1-(3-*hydroxy*-3,4-*dimethyloctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**17**) as a pale yellow gum (8.77 g, 77%) (Found: C, 57.75; H, 9.1; N, 15.3. $C_{13}H_{25}N_3O_3$ requires C, 57.5; H, 9.3; N, 15.5%); $\nu_{max.}$(film) 3 440 (OH), 3 100 (NH), 1 760 (NCO), and 1 680 cm^{-1} (NCO); δ_H (60 MHz; $CDCl_3$) 0.85—1.90 (19 H, m, chain), 3.03 (3 H, s, NCH_3), and 3.60—6.10 (2 H, t, NCH_2); *m/z* 271 (M^+, 2%), 253 (24), 186 (80), and 168 (100).

1-[(Z)-6-*Ethoxycarbonylhex*-2-*enyl*]-2-(3-*hydroxy*-3,4-*dimethyloctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**18**).—This compound was obtained as a gum in 60% yield by alkylation of (**17**) with ethyl (*Z*)-7-bromohept-5-enoate[17] using the method described for the preparation of compound (**10**) (Found: C, 61.7; H, 9.6; N, 10.0. $C_{22}H_{39}N_3O_5$ requires C, 62.1; H, 9.2; N, 9.9%); $\nu_{max.}$(film) 3 460 (OH), 1 765 (NCO), 1 735 (ester), and 1 710 cm^{-1} (NCO); δ_H (60 MHz; $CDCl_3$) 0.70—1.90 (23 H, m, chains), 2.00—2.60 [5 H, m, CH=CHCH_2, CH_2CO_2Et, and OH (exchanged with D_2O)], 3.06 (3 H, s, NCH_3), 3.50—3.95 (2 H, m, NCH_2), 4.00—4.40 (4 H, m, NCH_2CH=CH and $CO_2CH_2CH_3$), and 5.15—5.90 (2 H, m, CH=CH); *m/z* 425 (M^+, 3%), 380 (3), 340 (19), and 155 (100).

1-[(Z)-6-*Carboxyhex*-2-*enyl*]-2-(3-*hydroxy*-3,4-*dimethyloctyl*)-4-*methyl*-1,2,4-*triazolidine*-3,5-*dione* (**19**).—This compound was obtained as a viscous gum in 95% yield by hydrolysis of ester (**18**) using the method described for the preparation of compound (**6**) (Found: M^+, 397.2571. Calc. for $C_{20}H_{35}N_3O_5$: *M*, 397.2573); $\nu_{max.}$(film) 3 650—2 450 (OH), 1 765 (NCO), and 1 740—1 630 cm^{-1} (NCO and CO_2H); δ_H (60 MHz; $CDCl_3$) 0.72—1.95 (20 H, m, chains), 2.00—2.60 (4 H, m, CH_2CO_2H and CH=CHCH_2), 3.05 (3 H, s, NCH_3), 3.40—3.95 (2 H, m, NCH_2), 4.05 (2 H, d, NCH_2CH=CH), 5.10—5.90 (2 H, m, CH=CH), and 6.00 (2 H, br s, 2 × OH, exchanged with D_2O); *m/z* 397 (M^+, 4%), 312 (20), 294 (17), 253 (27), 168 (100), and 127 (88).

3,4-*Dimethyl*-1-(p-*tolylsulphonyloxy*)*octan*-3-*ol*.—A slurry of zinc (56 g, 0.86 mol), iodine (1 g), and dry benzene (12 ml) was stirred under reflux until the iodine vapour faded and then a portion (20 ml) of a mixture of ethyl bromoacetate (100 ml, 0.90 mol), 3-methylheptan-2-one (67 ml, 0.43 mol), and dry benzene (30 ml) was added. After vigorous reflux had commenced the remainder of the reactants was added dropwise, and the mixture

was heated under reflux for 0.5 h and allowed to cool to room temperature, and 20% sulphuric acid (350 ml) was added to the ice-cooled mixture. The product was extracted with ether (800 ml) and the extract was washed successively with water (4 × 400 ml) and brine (250 ml), and dried. Evaporation under reduced pressure yielded an orange oil which on distillation gave ethyl 3-hydroxy-3,4-dimethyloctanoate (45 g, 48%), b.p. 87—90 °C at 0.14 mmHg.

A solution of this ester (45 g, 0.21 mol) in dry ether (100 ml) was added to a stirred suspension of lithium aluminium hydride (10 g, 0.27 mol) in dry ether (200 ml) at 0 °C under nitrogen. The resulting mixture was heated under reflux for 1 h, and then cooled to 0 °C. The excess of hydride was destroyed by successive dropwise addition of water (10 ml), 10% aqueous sodium hydroxide (10 ml), and water (10 ml). The suspension was filtered through a pad of Kieselguhr and the filtrate was washed successively with water (200 ml) and brine (200 ml), and dried. Evaporation under reduced pressure gave 3,4-dimethyloctane-1,3-diol as an oil (34 g, 94%).

A solution of this alcohol (34 g, 0.20 mol) in dry pyridine (125 ml) was stirred at 0 °C, and toluene-*p*-sulphonyl chloride (39 g, 0.205 mol) was added. After 2 h at 0 °C the mixture was stored in a refridgerator for 18 h, and then poured into ice–water (800 ml). The product was extracted with ether (2 × 500 ml), and the combined extracts were washed successively with ice-cold 3M hydrochloric acid (4 × 250 ml), saturated aqueous sodium hydrogen carbonate (250 ml), and brine (250 ml), and dried. Evaporation under reduced pressure gave *3,4-dimethyl-1-(p-tolylsulphonyloxy)octan-3-ol* as a gum (56 g, 87%) (Found: C, 62.05; H, 9.0; S, 9.3. $C_{17}H_{28}O_4S$ requires C, 62.2; H, 8.6; S, 9.7%); $\nu_{max.}$(film) 3 540 (OH), 2 950 (CH), 1 360 and 1 180 cm^{-1} (SO_2–O); δ_H (60 MHz; $CDCl_3$) 0.68—1.60 (17 H, br m, chain), 1.77 (2 H, t, *J* 8 Hz, CH_2), 2.40 (3 H, s, CH_3), 4.17 (2 H, t, *J* 8 Hz, OCH_2), and 7.10—7.82 (4 H, q, *J* 8.5 Hz, C_6H_4).

3-Methyl-(1-p-tolylsulphonyloxy)nonan-3-ol.—This compound was obtained as a gum in 40% yield from octan-2-one using the method described above (Found: C, 62.4; H, 8.9. $C_{17}H_{28}O_4S$ requires C, 62.2; H, 8.6%); $\nu_{max.}$(film) 3 570 (OH), 2 950 (CH), 1 370 and 1 180 cm^{-1} (SO_2–O).

1-Bromo-3,4-dimethyloctan-3-ol.—A solution of 3,4-dimethyl-1-(*p*-tolylsulphonyloxy) octan-3-ol (21.1 g, 64.3 mmol) in dry acetone (350 ml) was stirred at 20 °C and powdered anhydrous lithium bromide (12.7 g, 0.15 mol) was added. The mixture was heated under reflux for 0.5 h and then allowed to cool to room temperature. The resultant precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residual oil was partitioned between ether (400 ml) and water (400 ml) and the organic phase was washed with brine (250 ml) and dried. Evaporation under reduced pressure gave *1-bromo-3,4-dimethyloctan-3-ol* as an oil (14.2 g, 93%), b.p. 75—80 °C at 0.1 mmHg (Found: C, 51.3; H 9.0; Br, 34.2%; ($M^+ - CH_3$), 221.0541. Calc. for $C_{10}H_{21}BrO$: C, 50.6; H, 8.9; Br, 33.7%; ($M - CH_3$), 221.0542); $\nu_{max.}$(film) 3 420 (OH), 2 970 (CH), and 650 cm^{-1} (C–Br); δ_H (60 MHz; $CDCl_3$) 0.69—1.70 (17 H, br m, chain), 2.03 (2 H, t, *J* 8 Hz, CH_2), and 3.48 (2 H, t, *J* 8 Hz, CH_2Br); *m/z* 221 [($M^+ - CH_3$), 2%], 151 (60), 129 (32), 84 (56), and 43 (100).

1-Bromo-3-methylnonan-3-ol.—Following the general method of synthesis described above, 1-bromo-3-methylnonan-3-ol was prepared in 94% yield from the corresponding tosylate, b.p. 96—98 °C at 1.0 mmHg; δ_H (60 MHz; $CDCl_3$) 0.87 (3 H, t, CH_3), 1.10—1.60 (14 H, m, chain), 2.00 (2 H, t, *J* 8 Hz, CH_2), and 3.43 (2 H, t, *J* 8 Hz, CH_2Br).

Ethyl (Z)-7-Bromohept-5-enoate.—A solution of ethyl 7-hydroxyhept-5-ynoate[17] (32 g, 0.19 mol) in ethanol (400 ml) containing quinoline (10 ml) was hydrogenated at atmospheric pressure over 5% Pd–$CaCO_3$ (3.2 g) until 1 mole equivalent of hydrogen had been taken up. The catalyst was removed by filtration through a pad of Kieselguhr and the filtrate was evaporated under reduced pressure. The residue (28 g) was dissolved in dry dichloromethane (400 ml) and triethylamine (35 ml), and the solution was stirred and cooled to −20 °C and methanesulphonyl chloride (16 ml, 0.21 mol) was added dropwise. The mixture was kept at −20 °C for 40 min, and then was washed successively with ice-cold 3M sulphuric acid (200 ml), saturated aqueous sodium hydrogen carbonate (200 ml), and brine (200 ml), and dried. Evaporation under reduced pressure gave ethyl (*Z*)-7-methylsulphonyloxyhept-5-enoate as an oil (34 g), $\nu_{max.}$(film) 2 940 (CH), 1 735 (ester), 1 660 (C=C), 1 350 and 1 175 cm^{-1} (SO_2–O); δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, t, $CO_2CH_2CH_3$), 1.50—2.60 (6 H, m, 3 × CH_2), 3.01 (3 H, s, CH_3SO_2), 5.82 (2 H, q, $CO_2CH_2CH_3$), 4.80 (2 H, d, OCH_2), and 5.30—6.05 (2 H, m, CH=CH).

The foregoing mesylate (34 g, 0.14 mol) was added to a solution of anhydrous lithium bromide (31 g, 0.35 mol) in dry acetone (500 ml) and the mixture was stirred at 25 °C for 18 h. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure and then partitioned between ether (500 ml) and water (500 ml). Work-up of the ether phase gave a brown oil which on chromatography on Kieselgel 60 (220 g) in chloroform gave ethyl (*Z*)-7-bromohept-5-enoate as a yellow oil (27 g, 61%) (Found: C, 46.3; H, 6.5. Calc. for $C_9H_{15}BrO_2$: C, 46.0; H, 6.4%); $\nu_{max.}$(film) 2 930 (CH), 1 735 (ester), 1 645 (C=C), and 740 cm^{-1} (C–Br); δ_H (60 MHz; $CDCl_3$) 1.25 (3 H, t, $CO_2CH_2CH_3$), 1.50—2.50 (6 H, m, 3 × CH_2), 3.87—4.40 (4 H, m, $CO_2CH_2CH_3$ and $BrCH_2$), and 5.33—6.00 (2 H, m, CH=CH).

Preparation of Vinyl Ketones.—Oct-1-en-3-one. Freshly distilled vinyl bromide (160 g, 1.5 mol) was added to a stirred slurry of magnesium turnings (32.5 g, 1.34 mol) in dry tetrahydrofuran (THF) (200 ml) under nitrogen. After completion of addition, the mixture was stirred for 0.5 h and then a solution of hexanal (100 g, 1 mol) in dry THF (300 ml) was added dropwise to the ice-cooled solution. The mixture was stirred at room temperature overnight and then was poured into saturated aqueous ammonium chloride (500 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 × 200 ml). The combined organic layers were evaporated to dryness and distillation of the residue gave oct-1-en-3-ol as an oil (96.5 g), b.p. 79—80 °C at 16 mmHg.

4M Jones chromic acid reagent[22] (320 ml) was added dropwise to a stirred solution of the foregoing alcohol (96.5 g, 0.75 mol) in acetone (300 ml) at 0 °C until a permanent orange colour remained. Water (1.5 l) was added followed by sodium metabisulphite (25 g) and the mixture was extracted with ether (3 × 300 ml) to remove the product. Evaporation of the extracts followed by distillation under reduced pressure gave oct-1-en-3-one as a pale yellow oil (61 g, 64%), b.p. 60—66 °C at 16 mmHg (lit.,[23] 63—65 °C at 14 mmHg).

Non-1-en-3-one. This compound was prepared from heptanal in a similar way to that described above, b.p. 82—84 °C at 14 mmHg (lit.,[24] 85—87 °C at 35 mmHg).

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