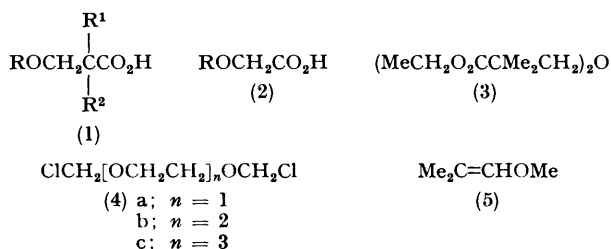


## Preparation of Polyether Polycarboxylic Acids containing Quaternary Carbon Atoms in the Backbone

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The addition of chloromethyl ethers (4a—c), (10a), and (11a) to 1-methoxy-2-methylprop-1-ene (5) is catalysed by mercury(II) chloride. Hydrolysis of the resulting chloro-ethers [e.g. (6a)] gives 3-alkoxy-2,2-dialkylpropanals [e.g. (7a)] which can be oxidised to the corresponding carboxylic acids [e.g. (8a)] with hydrogen peroxide in the presence of selenium dioxide as catalyst. Poly(alkoxyacetic) acids have been obtained by reaction of alkoxides with *NN*-dialkylchloroacetamides followed by hydrolysis. Thus the acids (12a—c) have been obtained from 2,2-dimethylpropane-1,3-diol, 2-hydroxymethyl-2-methylpropane-1,3-diol, and pentaerythritol, respectively.

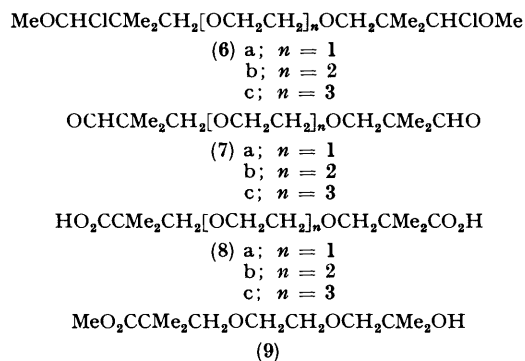
OVER the past decade the complexation of cations by polyoxygenated ligands has attracted steadily increasing attention. Much of this attention has stemmed from an interest in biological phenomena involving ion selectivity and transport and in the catalytic activity of complexes containing such ligands. These ligands may be charged, for example the carboxylate ionophores such as ionomycin,<sup>1</sup> or neutral, as in the crown ethers<sup>2</sup> and cryptands.<sup>3</sup> As a part of our investigations of the synthesis and complexing properties of potentially polydentate ligands containing quaternary carbon atoms in the backbone, we have devised routes to a range of polyether polycarboxylic acids. An earlier approach, involving oxetan derivatives, to a ligand of this type, and the preparation therefrom of macrocyclic copper chelates, have been described.<sup>4</sup> This paper deals with synthetic procedures which result in the conversion of primary alcohols into either 3-alkoxy-2,2-dialkylpropionic acids (1) or 2-alkoxyacetic acids (2).



For the synthesis of the former acids (1), two variants of a similar approach were initially considered. Both involve nucleophilic displacement of the halogen from chloromethyl ethers. In one of them the  $\alpha$ -anion derived from a dialkylacetic acid derivative would serve as the nucleophile. Such a species could be generated by deprotonation of a suitable derivative with, for example, lithium di-isopropylamide<sup>5</sup> or from an  $\alpha$ -halogeno derivative by the Reformatsky reaction. Indeed, diethyl 2,2,6,6-tetramethyl-4-oxaheptanedioate (3) has been prepared<sup>6</sup> from bis(chloromethyl) ether and ethyl 2-bromo-2-methylpropanoate using Reformatsky conditions. In the second approach, it was anticipated that enol ethers might serve as nucleophiles if the reactivity of the chloroether were enhanced by the use of a Lewis acid. The products in this case, after hydrolysis, would be the aldehydes, which could then be oxidised to the

required acids. This second approach was chosen since it appeared to be more suitable for the preparation of relatively large quantities of these acids and because of the potential versatility of the intermediate aldehydes in the synthesis of other polydentate ligands, including macrocycles.

The condensation of 1,2-bis(chloromethoxy)ethane (4a) with 1-methoxy-2-methylprop-1-ene (5) was first investigated. Mercury(II) chloride was used as catalyst since we anticipated that, of the common Lewis acids, it would give the best selectivity for abstraction of chloride *versus* alkoxide. It is well known<sup>7</sup> that, for example in reactions of chloromethyl methyl ether with aromatic systems, aluminium chloride, tin(IV) chloride, or zinc chloride catalyses chloromethylation rather than methoxymethylation. Indeed, reaction of (4a) with (5) in the presence of mercury(II) chloride is exothermic and was moderated by cooling in an ice-bath. <sup>1</sup>H N.m.r. spectroscopy of the product mixture suggested that complete and clean conversion into the desired bis(chloro-ether) (6a) had occurred.† Hydrolysis with ice-cold aqueous sodium hydrogencarbonate gave 2,2,9,9-tetramethyl-4,7-dioxadecanedial (7a) which decomposed on attempted distillation and was therefore characterised as its bis-2,4-dinitrophenylhydrazone [79% yield from (4a)]. The dialdehyde (7a), upon oxidation in aqueous



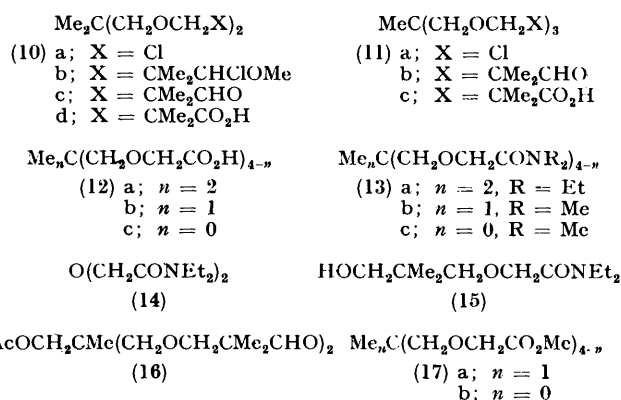
methanol with hydrogen peroxide in the presence of selenium dioxide as catalyst<sup>8</sup> gave the diacid (8a), m.p. 85—86 °C [47% recovered yield from (4a)]. A sample

† More complex product mixtures (<sup>1</sup>H n.m.r.) were obtained when zinc chloride, tin(IV) chloride, or boron trifluoride-ether was used as catalyst.

of the residue from crystallisation of the diacid was esterified with diazomethane and separated into two major fractions by preparative t.l.c. One of these was identical (<sup>1</sup>H n.m.r. and t.l.c.) with the product of methylation of (8a). The other appears to be (<sup>1</sup>H n.m.r. of it and of the derived oily 3,5-dinitrobenzoate) methyl 9-hydroxy-2,2,9-trimethyl-4,7-dioxadecanoate (9), the parent acid presumably having resulted from decarbonylation during the oxidation step.

The diacids (8b), (8c), and (10d), and the triacid (11c) were prepared by similar procedures. The last two were obtained as crystalline solids, while the first two were purified by distillation of the derived methyl esters. In addition, (8b) was purified as its barium salt.

Two groups have reported<sup>9,10</sup> the preparation of a range of poly(alkoxyacetic) acids. In the earlier work<sup>9</sup> involving the diacids HO<sub>2</sub>CCH<sub>2</sub>[OCH<sub>2</sub>CH<sub>2</sub>]<sub>n</sub>OCH<sub>2</sub>CO<sub>2</sub>H (*n* = 0–3), the two highest members of the series (*n* = 2, 3) were prepared by hydrolysis of the esters resulting from reaction of methyl chloroacetate with the disodium derivatives of diethylene glycol and triethylene glycol. In the more recent work<sup>10</sup> alkoxyacetic acids derived from neopentyl-type polyols have been obtained by



treatment of these polyols with ethyl diazoacetate in the presence of boron trifluoride-ether, followed by hydrolysis of the resulting esters.

We have synthesised acids of the latter type, namely 5,5-dimethyl-3,7-dioxanonanedioic acid (12a)<sup>10</sup> and the related tri- and tetra-acids (12b) and (12c) by the successive addition of the appropriate polyol and of *NN*-diethyl- or *NN*-dimethyl-chloroacetamide to sodium t-pentoxide in t-pentyl alcohol followed by hydrolysis of the amides (13) formed. Attempts to prepare ester analogues of (13a) by using methyl chloroacetate, t-butyl chloroacetate, or ethyl bromoacetate in place of the *NN*-diethylchloroacetamide were unsuccessful (see Experimental section). We have not attempted these reactions in xylene (*cf.* ref. 9) since it was anticipated that attempts to generate sodium alkoxides by heating neopentyl-type polyols with sodium would result in extensive decomposition.<sup>11</sup> During the preparation of (13a) it was found that better yields were obtained if the acetamide residues were introduced stepwise, *i.e.* initially 2,2-dimethylpropane-1,3-diol was added to one molar equivalent of sodium t-

pentoxide followed by one molar equivalent of *NN*-diethylchloroacetamide. After the resulting exothermic reaction had subsided further molar equivalents of the last two reagents were added. In this case the diamide was recovered in good yield (83%) by distillation along with a fore-run which contained *NNN'*-tetraethyl-3-oxapentanediamide (14) and *NN*-diethyl-6-hydroxy-5,5-dimethyl-3-oxahexanamide (15). The yields of the tri- and tetra-amides were substantially lower (30–40%). In all three cases base hydrolysis was slow but quantitative.

#### EXPERIMENTAL

<sup>1</sup>H N.m.r. spectra were run on Varian A-60A or Bruker WP-60 spectrometers in CDCl<sub>3</sub> solution unless otherwise indicated. Melting points were determined on a Kofler hot-stage apparatus. Elemental analyses were obtained from Guelph Chemical Laboratories Ltd., Guelph, Ontario, or from Galbraith Laboratories Inc., Knoxville, Tenn., U.S.A.

*Chloromethyl Ethers.*—The chloro-ethers (4a), (4b), (10a) and (11a),<sup>12</sup> and (4c)<sup>13</sup> were prepared by reaction<sup>12</sup> of hydrogen chloride gas with a mixture of paraformaldehyde and the appropriate polyol.

*2,2,9,9-Tetramethyl-4,7-dioxadecanedioic Acid (8a).*—1-Methoxy-2-methylprop-1-ene (5) (47.3 g, 0.550 mol) was added dropwise over 15 min to 1,2-bis(chloromethoxy)ethane (4a) (39.8 g, 0.250 mol) containing mercury(II) chloride (1.36 g, 5.0 × 10<sup>-3</sup> mol) with stirring and cooling in ice-water. The reaction solution darkened during the addition and finally became amber. The temperature was allowed to rise to ambient during 2 h, after which time <sup>1</sup>H n.m.r. indicated that the vinyl ether had been completely consumed to give essentially pure 3,12-dichloro-4,4,11,11-tetramethyl-2,6,9,13-tetraoxatetradecane (6a); δ 1.04 (s, 12 H, CMe), 3.43 (s, 4 H, neopentyl CH<sub>2</sub>), 3.61 (s, 6 H, OMe), 3.64 (s, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O), and 5.61 (s, 2 H, CHCl). This intermediate was hydrolysed by stirring with ice-water, the liberated acid being neutralised by gradual addition of sodium hydrogencarbonate (42 g, 0.50 mol). The organic layer was separated, combined with an ether extract of the aqueous layer, and dried over anhydrous sodium sulphate. Removal of the drying agent and the ether left the essentially pure dialdehyde (7a) (54 g), as a pale yellow oil; δ 1.02 (s, 12 H, CMe), 3.41 (s, 4 H, neopentyl CH<sub>2</sub>), 3.48 (s, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O), and 9.45 (s, 2 H, CHO). Since attempted distillation of this compound resulted in its partial decomposition (new peaks appeared in the <sup>1</sup>H n.m.r. spectrum of the distillate), it was characterised as the *bis*-2,4-dinitrophenylhydrazone, m.p. 201–203 °C (from acetic acid); δ 1.21 (s, 12 H, CMe), 3.43 (s, 4 H, neopentyl CH<sub>2</sub>), 3.63 (s, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O), 7.54 (s, 2 H, CH=N), 7.88 (d, *J* 9.5 Hz, 2 H, aromatic 6-H), 8.30 (dd, *J* 9.5 and 2.5 Hz, 2 H, aromatic 5-H), 9.09 (d, *J* 2.5 Hz, 2 H, aromatic 3-H), and 10.96 (br s, 2 H, NH) (Found: C, 48.75; H, 5.15; N, 19.35. C<sub>24</sub>H<sub>30</sub>N<sub>8</sub>O<sub>10</sub> requires C, 48.8; H, 5.15; N, 19.0%). The dialdehyde (7a) (54 g) in aqueous methanol (200 cm<sup>3</sup>; 1 : 1 v/v), to which selenium dioxide (1.0 g) had been added, was oxidised by the addition of 30% aqueous hydrogen peroxide (60 g, 0.55 mol) in five portions over 1 h. Although an exothermic reaction took place, the mixture did not require cooling. The resulting mixture was stirred at ambient temperature overnight and then the solvent was

distilled out, finally under vacuum. Residual water was removed from the product by co-evaporation with toluene to leave an almost colourless gum, which partially crystallised on standing. Crystallisation from ether-hexane afforded clumps of irregularly shaped colourless crystals of 2,2,9,9-tetramethyl-4,7-dioxadecanedioic acid (8a) [30.5 g, 46.5% based on (4a)]. This solid turned pale pink on standing in light presumably due to the presence of selenium-containing impurities. Recrystallisation from acetone-hexane gave material of m.p. 85–86 °C;  $\delta$  1.17 (s, 12 H, CMe), 3.42 (s, 4 H, neopentyl CH<sub>2</sub>), 3.54 (s, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O) and 11.59 (s, 2 H, CO<sub>2</sub>H) (Found: C, 54.8; H, 8.55. C<sub>12</sub>H<sub>22</sub>O<sub>6</sub> requires C, 54.95; H, 8.45%). A portion (465 mg) of the residual gum (31.7 g) from the mother-liquors of the initial crystallisation was methylated with an excess of diazomethane. Preparative t.l.c. (acetone-toluene, 3:17 v/v) of the product (502 mg) gave two major bands. The less polar one gave material (180 mg) identical (t.l.c., <sup>1</sup>H n.m.r.) with the product from esterification of (8a) with diazomethane. The more polar band gave an oil (9) (165 mg);  $\delta$  1.24 (s, 12 H, CMe), 2.67 (br s, 1 H, OH, lost on D<sub>2</sub>O equilibration), 3.28 (s, 2 H, a neopentyl CH<sub>2</sub>), 3.47 (s, 2 H, a neopentyl CH<sub>2</sub>), 3.60 (narrow m, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O), and 3.65 (s, 3 H, CO<sub>2</sub>Me). The derived (3,5-dinitrobenzoyl chloride-pyridine) 3,5-dinitrobenzoate was also an oil, even after preparative t.l.c. (acetone-toluene, 3:37 v/v);  $\delta$  1.13 (s, 6 H, CMe), 1.67 (s, 6 H, OMe), 3.47 (s, 2 H, neopentyl CH<sub>2</sub>), 3.68 (s, 7 H, OMe + OCH<sub>2</sub>CH<sub>2</sub>O), 3.80 (s, 2 H, neopentyl CH<sub>2</sub>), and 9.17 (m, 3 H, aromatic).

**2,2,12,12-Tetramethyl-4,7,10-trioxatridecanedioic Acid (8b).**—The mercury(II) chloride (1.36 g, 5.0 × 10<sup>-3</sup> mol) catalysed reaction of 1-methoxy-2-methylprop-1-ene (5) (47.3 g, 0.550 mol) with bis-2-(chloromethoxy)ethyl ether (50.8 g, 0.250 mol) when carried out as outlined above did not go to completion (<sup>1</sup>H n.m.r.) until additional mercury(II) chloride (0.68 g, 2.5 × 10<sup>-3</sup> mol) was added and the resulting mixture was stirred at ambient temperature overnight. The intermediate, 3,15-dichloro-4,4,14,14-tetramethyl-2,6,9,12,16-pentaoxaheptadecane (6b),  $\delta$  1.02 (s, 12 H, CMe), 3.35 (s, 4 H, neopentyl CH<sub>2</sub>), 3.51 (s, 6 H, OMe), 3.60 (br s, 8 H, OCH<sub>2</sub>CH<sub>2</sub>O), and 5.55 (s, 2 H, CHCl), was hydrolysed as before to give an almost pure sample of the dialdehyde (7b),  $\delta$  1.05 (s, 12 H, CMe), 3.50 (s, 4 H, neopentyl CH<sub>2</sub>), 3.58 (s, 8 H, OCH<sub>2</sub>CH<sub>2</sub>O), and 9.59 (s, 2 H, CHO), the *bis*-2,4-dinitrophenylhydrazone of which had m.p. 156–158 °C (from acetic acid);  $\delta$  1.21 (s, 12 H, CMe), 3.49 (s, 4 H, neopentyl CH<sub>2</sub>), 3.64 (s, 8 H, OCH<sub>2</sub>CH<sub>2</sub>O), 7.61 (s, 2 H, CH=N), 7.88 (d, *J* 9.5 Hz, 2 H, aromatic 6-H), 8.25 (dd, *J* 9.5 and 2.5 Hz, 2 H, aromatic 5-H), 9.04 (d, *J* 2.5 Hz, 2 H, aromatic 3-H), and 10.95 (br s, 2 H, NH) (Found: C, 49.15; H, 5.5; N, 17.55. C<sub>26</sub>H<sub>34</sub>N<sub>8</sub>O<sub>11</sub> requires C, 49.2; H, 5.4; N, 17.65%). The dialdehyde (7b) was oxidised as above with hydrogen peroxide in the presence of selenium dioxide and on work-up gave an almost colourless gum (60.4 g). Since attempts to induce crystallisation of the required diacid (8b) were unsuccessful, the crude product was converted into either the dimethyl ester or the barium salt, each of which was subsequently obtained in pure form as outlined in (i) and (ii) respectively.

(i) A solution of the crude acid (60.4 g) in methanol (150 cm<sup>3</sup>) containing toluene-*p*-sulphonic acid monohydrate (0.95 g) was heated at reflux for 1 h after which the solution was allowed to cool and trimethyl orthoformate (60 cm<sup>3</sup>) was added. After standing overnight at ambient temperature, an excess of potassium carbonate was added

to neutralise the catalyst. Most of the excess of methanol and volatiles were then evaporated off, and the residue was filtered and distilled to give *dimethyl 2,2,12,12-tetramethyl-4,7,10-trioxatridecanedioate* [32.1 g, 38.4% based on (4b)], b.p. 123–127 °C at 0.005 mmHg. This material contained small amounts of selenium (red powder) and a more polar (t.l.c.) product. Purification of a sample (600 mg) by preparative t.l.c. (acetone-toluene, 3:17 v/v) gave one major band (552 mg), which was distilled on a sublimation block (125–135 °C at 0.005 mmHg);  $\delta$  1.18 (s, 12 H, CMe), 3.48 (s, 4 H, neopentyl CH<sub>2</sub>), 3.59 (s, 8 H, OCH<sub>2</sub>CH<sub>2</sub>O), and 3.68 (s, 6 H, OMe) (Found: C, 57.55; H, 8.95. C<sub>16</sub>H<sub>30</sub>O<sub>7</sub> requires C, 57.45; H, 9.05%).

(ii) Barium carbonate (52 g) was added in portions with stirring to the crude diacid (74.4 g) suspended in water (300 cm<sup>3</sup>). When evolution of carbon dioxide had subsided, the mixture was heated on a steam-bath with occasional swirling for 2 h. The resulting aqueous solution was decanted from a residual oily coagulation. The residue was washed several times with water and the combined aqueous solutions were treated with decolourising carbon, filtered, and evaporated to give a red-brown gum. This gum dissolved to a considerable extent in hot toluene (600 cm<sup>3</sup>) and solution was completed when ethanol (50 cm<sup>3</sup>) was added. Water and ethanol were then removed by distillation as their azeotropes with toluene to leave a clear dark solution (500 cm<sup>3</sup>). On standing overnight, a dark gum [which solidified to a glass (23.9 g) on drying *in vacuo*] separated out, leaving a light yellow solution. The <sup>1</sup>H n.m.r. spectrum of this glass in deuterium oxide was identical with that of the pure barium salt (see below). Prolonged standing (6 weeks) of the supernatant led to the gradual deposition of a white powdery solid (27.4 g) which proved to be *barium 2,2,12,12-tetramethyl-4,7,10-trioxatridecanedioate*, m.p. 284–286 °C; (D<sub>2</sub>O, acetone internal standard) —1.15 (s, 12 H, CMe), 1.32 (s, 4 H, neopentyl CH<sub>2</sub>), and 1.48 (s, 8 H, OCH<sub>2</sub>CH<sub>2</sub>O) (Found: C, 38.0; H, 5.55. C<sub>14</sub>H<sub>24</sub>BaO<sub>7</sub> requires C, 38.05; H, 5.5%).

**2,2,15,15-Tetramethyl-4,7,10,13-tetraoxahexadecanedioic Acid (8c).**—As previously, the mercury(II) chloride (2 g) catalysed reaction of 1-methoxy-2-methylprop-1-ene (5) (51.0 g, 0.593 mol) with 1,2-bis-[2-(chloromethoxy)ethoxy]ethane (4c) (66.5 g, 0.269 mol) did not go to completion (<sup>1</sup>H n.m.r.) until additional mercury(II) chloride (1 g) was added. The product, 3,18-dichloro-4,4,17,17-tetramethyl-2,6,9,12,15,19-hexaoxacosane (6c),  $\delta$  1.02 (s, 12 H, CMe), 3.37 (s, 4 H, neopentyl CH<sub>2</sub>), 3.54 (s, 6 H, OMe), 3.64 (br s, 8 H, OCH<sub>2</sub>CH<sub>2</sub>O), 3.69 (s, 4 H, OCH<sub>2</sub>CH<sub>2</sub>O) and 5.60 (s, 2 H, CHCl), was hydrolysed as before to give an essentially pure sample of the dialdehyde (7c) (81.5 g),  $\delta$  1.05 (s, 12 H, CMe), 3.51 (s, 4 H, neopentyl CH<sub>2</sub>), 3.62 (br s, 12 H, OCH<sub>2</sub>CH<sub>2</sub>O) and 9.63 (s, 2 H, CHO), the *bis*-2,4-dinitrophenylhydrazone of which had m.p. 144–147 °C (from acetic acid);  $\delta$  1.22 (s, 12 H, CMe), 3.46 (s, 4 H, neopentyl CH<sub>2</sub>), 3.65 (s, 12 H, OCH<sub>2</sub>CH<sub>2</sub>O), 7.58 (s, 2 H, CH=N), 7.85 (d, *J* 9 Hz, 2 H, aromatic 6-H), 8.23 (dd, *J* 9 and 2.4 Hz, 2 H, aromatic 5-H), 9.02 (d, *J* 2.4 Hz, 2 H, aromatic 3-H) and 10.94 (br s, 2 H, NH) (Found: C, 49.7; H, 5.6; N, 16.35. C<sub>28</sub>H<sub>38</sub>N<sub>8</sub>O<sub>12</sub> requires C, 49.55; H, 5.65; N, 16.5%). The dialdehyde (7c) was oxidised as before, work-up giving an almost colourless syrup which did not crystallise. Esterification with methanol-toluene-*p*-sulphonic acid-trimethyl orthoformate gave *dimethyl 2,2,15,15-tetramethyl-4,7,10,13-tetraoxahexadecanedioate* [48.9 g, 47.5% based on (4c)], b.p. 140–150 °C at 0.005 mmHg. A sample (640 mg) of this material was

purified by preparative t.l.c. (acetone-toluene, 3:17 v/v) giving one major band (531 mg) and more polar material (31 mg). The former was distilled on a sublimation block (150–170 °C at 0.005 mmHg);  $\delta$  1.17 (s, 12 H, CMe), 3.47 (s, 4 H, neopentyl CH<sub>2</sub>), 3.62 (narrow m, 12 H, OCH<sub>2</sub>CH<sub>2</sub>O) and 3.67 (s, 6 H, OMe) (Found: C, 57.1; H, 9.1. C<sub>18</sub>H<sub>34</sub>O<sub>8</sub> requires C, 57.15; H, 9.05%).

2,2,6,6,10,10-Hexamethyl-4,8-dioxaundecanedioic Acid (10d).—1-Methoxy-2-methylprop-1-ene (5) (63.0 g, 0.732 mol) reacted smoothly with 1,3-bis(chloromethoxy)-2,2-dimethylpropane (10a) (70.0 g, 0.348 mol) in the presence of mercury(II) chloride (2.0 g) to give essentially pure (<sup>1</sup>H n.m.r.) 3,13-dichloro-4,4,8,8,12,12-hexamethyl-2,6,10,14-tetraoxapentadecane (10b),  $\delta$  0.88 (s, 6 H, central CMe), 1.01 (s, 12 H, terminal CMe), 3.15 (s, 4 H, central neopentyl CH<sub>2</sub>), 3.27 (s, 4 H, terminal neopentyl CH<sub>2</sub>), 3.52 (s, 6 H, OMe), and 5.54 (s, 2 H, CHCl). Hydrolysis as before gave the derived aldehyde (10c),  $\delta$  0.92 (s, 6 H, central CMe), 1.11 (s, 12 H, terminal CMe), 3.14 (s, 4 H, central neopentyl CH<sub>2</sub>), 3.40 (s, 4 H, terminal neopentyl CH<sub>2</sub>) and 9.63 (s, 2 H, CHO), the *bis*-2,4-dinitrophenylhydrazone of which had m.p. 168–170 °C (from acetic acid),  $\delta$  0.92 (s, 6 H, central CMe), 1.21 (s, 12 H, terminal CMe), 3.23 (s, 4 H, central neopentyl CH<sub>2</sub>), 3.37 (s, 4 H, terminal neopentyl CH<sub>2</sub>), 7.57 (s, 2 H, CH=N), 7.93 (d, *J* 9.4 Hz, 2 H, aromatic 6-H), 8.33 (dd, *J* 9.4 and 2.5 Hz, 2 H, aromatic 5-H), 9.11 (d, *J* 2.5 Hz, 2 H, aromatic 3-H), and 10.95 (br s, 2 H, NH) (Found: C, 51.25; H, 5.75; N, 17.65. C<sub>27</sub>H<sub>36</sub>N<sub>8</sub>O<sub>10</sub> requires C, 51.25; H, 5.75; N, 17.7%). Oxidation of the dialdehyde (10c) as before gave a white solid, which, on crystallisation from hexane, afforded pure 2,2,6,6,10,10-hexamethyl-4,8-dioxaundecanedioic acid (10d) (46.7 g, 44.1% based on (10a), m.p. 96–97 °C,  $\delta$  0.82 (s, 6 H, central CMe), 1.17 (s, 12 H, terminal CMe), 3.15 (s, 4 H, central neopentyl CH<sub>2</sub>), 3.38 (s, 4 H, terminal neopentyl CH<sub>2</sub>), and 11.04 (s, 2 H, CO<sub>2</sub>H) (Found: C, 59.45; H, 9.55. C<sub>15</sub>H<sub>28</sub>O<sub>6</sub> requires C, 59.2; H, 9.25%).

1,1,1-Tris(4-carboxy-4-methyl-2-oxapentyl)ethane (11c).—Reaction of 1-methoxy-2-methylprop-1-ene (5) (11.5 g, 0.134 mol) with 1,1,1-tris(chloromethoxymethyl)ethane (11a) (11.3 g, 0.0425 mol) in the presence of mercury(II) chloride (0.3 g) followed by hydrolysis afforded the crude trialdehyde (11b) (16.5 g), a sample (0.248 g) of which was treated with an excess of 2,4-dinitrophenylhydrazine in acidic methanol. Preparative t.l.c. (dichloromethane) of the product gave three main fractions. The least polar (0.165 g) of these was the *tris*-2,4-dinitrophenylhydrazone of (11b), which had m.p. 124–125 °C (from dichloromethane-methanol),  $\delta$  0.96 (s, 3 H, central CMe), 1.20 (s, 18 H, terminal CMe), 3.32 (br s, 12 H, neopentyl CH<sub>2</sub>), 7.51 (s, 3 H, CH=N), 7.86 (d, *J* 9.5 Hz, 3 H, aromatic 6-H), 8.26 (dd, *J* 9.5 and 2.6 Hz, 3 H, aromatic 5-H), 9.05 (d, *J* 2.6 Hz, 3 H, aromatic 3-H), and 10.93 (br s, 3 H, NH) (Found: C, 50.15; H, 5.35; N, 18.35. C<sub>38</sub>H<sub>48</sub>N<sub>12</sub>O<sub>15</sub> requires C, 50.0; H, 5.3; N, 18.4%). The fraction (0.109 g) of intermediate polarity was the *bis*-2,4-dinitrophenylhydrazone of (11b), m.p. 139–141 °C (from dichloromethane-methanol),  $\delta$  0.91 (s, 3 H, central CMe), 1.05 (s, 6 H, CMe  $\alpha$  to CHO), 1.20 (s, 12 H, CMe  $\alpha$  to CH=N), 3.24, 3.30, and 3.36 (all s, 12 H, neopentyl CH<sub>2</sub>), 7.51 (s, 2 H, CH=N), 7.89 (d, *J* 9.7 Hz, 2 H, aromatic 6-H), 8.29 (dd, *J* 9.7 and 2.4 Hz, 2 H, aromatic 5-H), 9.09 (d, *J* 2.4 Hz, 2 H, aromatic 3-H), 9.51 (s, 1 H, CHO), and 10.97 (br s, 2 H, NH) (Found: C, 52.25; H, 6.1; N, 15.25. C<sub>32</sub>H<sub>44</sub>N<sub>8</sub>O<sub>12</sub> requires C, 52.45; H, 6.05; N, 15.3%). The most polar

fraction (0.048 g) on treatment with acetic anhydride-pyridine afforded the *bis*-2,4-dinitrophenylhydrazone of (16), m.p. 123–126 °C (from dichloromethane-methanol),  $\delta$  0.97 (s, 3 H, central CMe), 1.20 (s, 12 H, terminal CMe), 2.03 (s, 3 H, O<sub>2</sub>CMe), 3.30 and 3.33 (each s, 8 H, neopentyl CH<sub>2</sub>), 4.01 (s, 2 H, CH<sub>2</sub>OAc), 7.50 (s, 2 H, CH=N), 7.89 (d, *J* 9.5 Hz, 2 H, aromatic 6-H), 8.29 (dd, *J* 9.5 and 2.4 Hz, 2 H, aromatic 5-H), 9.09 (d, *J* 2.4 Hz, 2 H, aromatic 3-H), and 10.97 (br s, 2 H, NH) (Found: C, 50.55; H, 5.65; N, 16.15. C<sub>29</sub>H<sub>38</sub>N<sub>8</sub>O<sub>12</sub> requires C, 50.45; H, 5.55; N, 16.25%). Oxidation of the crude trialdehyde (11b) (16.25 g) and work-up as before gave a heavy syrup from which crystalline material deposited on standing. Trituration with hexane-ether (4:1 v/v), followed by cooling in a refrigerator (12 h) and then filtration gave slightly discoloured crystals [3.95 g, 22% based on (11a)] of 1,1,1-tris(4-carboxy-4-methyl-2-oxapentyl)ethane (11c), m.p. 124–127 °C (from acetone-hexane);  $\delta$  0.91 (s, 3 H, central CMe), 1.22 (s, 18 H, terminal CMe), 3.23 (s, 6 H, central neopentyl CH<sub>2</sub>), 3.36 (s, 6 H, terminal neopentyl CH<sub>2</sub>) and 10.61 (br s, 3 H, CO<sub>2</sub>H) (Found: C, 57.25; H, 8.65. C<sub>20</sub>H<sub>36</sub>O<sub>9</sub> requires C, 57.15; H, 8.65%).

5,5-Dimethyl-3,7-dioxanonanedioic Acid (12a).—Sodium t-pentoxide was prepared by dissolving sodium (12.0 g, 0.522 mol) in refluxing t-pentyl alcohol (500 cm<sup>3</sup>) under nitrogen. A solution of 2,2-dimethylpropane-1,3-diol (52.0 g, 0.500 mol) in t-pentyl alcohol (400 cm<sup>3</sup>) was added to the cooled mixture with stirring, followed by the addition of *NN*-diethylchloroacetamide (77.0 g, 0.515 mol) in one portion. A moderately exothermic reaction took place and the stirring was continued for 2 h. Further quantities of sodium t-pentoxide [from sodium (12.0 g) in t-pentyl alcohol (500 cm<sup>3</sup>)] and the amide (77.0 g) were then added. Again an exothermic reaction was noted and when this had subsided, the mixture was heated to reflux for 2 h. Most of the solvent was distilled off and water (200 cm<sup>3</sup>) was added to the residue. Extraction with ether gave an oil which was distilled at 0.005 mmHg to give pure *NNN'*-tetraethyl-5,5-dimethyl-3,7-dioxanonanediamide (13a) (138.2 g, 83.6% based on starting diol), b.p. 166 °C,  $\delta$  0.92 (s, 6 H, quaternary CMe), 1.16 (br t, *J* 7.0 Hz, 12 H, CH<sub>2</sub>Me), 3.29 (s, 4 H, neopentyl CH<sub>2</sub>), 3.38 (q, *J* 7.0 Hz, 8 H, NCH<sub>2</sub>), and 4.10 (s, 4 H, OCH<sub>2</sub>CO) (Found: C, 61.6; H, 10.35; N, 8.55. C<sub>17</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub> requires C, 61.8; H, 10.35; N, 8.5%). Redistillation of the fore-run (28.0 g), b.p. 76–166 °C, gave *NN*-diethyl-6-hydroxy-5,5-dimethyl-3-oxahexanamide (15) (8.5 g), b.p. 103–104 °C,  $\delta$  0.85 (s, 6 H, quaternary CMe), 1.12 and 1.16 (both t, *J* 7 Hz, 6 H, CH<sub>2</sub>Me), 3.24 (s, 2 H, neopentyl CH<sub>2</sub>OC), 3.24 and 3.39 (each q, *J* 7 Hz, 4 H, NCH<sub>2</sub>), 3.40 (s, 2 H, CH<sub>2</sub>OH), 4.11 (s, 2 H, OCH<sub>2</sub>CO), and 4.50 (br s, 1 H, OH; lost on D<sub>2</sub>O equil.) (Found: C, 60.65; H, 10.7; N, 6.6. C<sub>11</sub>H<sub>23</sub>NO<sub>3</sub> requires C, 60.8; H, 10.65; N, 6.45%). Preparative t.l.c. (ethyl acetate) of a sample of the fore-run from this second distillation gave *NNN'*-tetraethyl-3-oxapentanediamide (14) as a major polar band  $\delta$  1.15 (br t, *J* 7 Hz, 6 H, CH<sub>2</sub>Me), 3.37 (br q, *J* 7 Hz, 4 H, NCH<sub>2</sub>), and 4.28 (s, 4 H, OCH<sub>2</sub>CO). The diamide (13a) (124.8 g, 0.378 mol) was hydrolysed by prolonged (5 days) heating with sodium hydroxide (40 g, 1.0 mol) in water (300 cm<sup>3</sup>). Daily, ca. 100 cm<sup>3</sup> of aqueous diethylamine was allowed to distill out, and water (100 cm<sup>3</sup>) was added. The resulting solution was acidified with an excess of concentrated hydrochloric acid, evaporated to dryness, and the residue thus obtained was extracted with acetone. The recovered known <sup>10</sup> acid (12a) was crystallised from toluene

to give material (76.2 g, 91.5% based on diamide) having m.p. 57–59 °C.

**1,1,1-Tris-(3-carboxy-2-oxapropyl)ethane (12b).**—Reaction of 2-hydroxymethyl-2-methylpropane-1,3-diol (12.0 g, 0.100 mol) in three steps with sodium *t*-pentoxide and *NN*-dimethylchloroacetamide with work-up as above gave a dark gum (36.4 g). Preparative t.l.c. (ethanol–ethyl acetate, 1 : 9 v/v) of a sample (400 mg) of this gum gave, as the most polar fraction, the triamide (13b) (229 mg), which failed to crystallise;  $\delta$  0.92 (s, 3 H, CMe), 2.85 and 2.91 (s, 18 H, NMe), 3.32 (s, 6 H, neopentyl CH<sub>2</sub>), and 4.01 (s, 6 H, OCH<sub>2</sub>CO). Hydrolysis of the remainder of the dark gum and work-up as above gave a syrup (27.4 g) which did not crystallise and was therefore esterified with methanol–toluene-*p*-sulphonic acid–trimethylorthoformate (see above). Distillation of the resulting oil (27.0 g) at 0.005 mmHg gave **1,1,1-tris-(3-methoxycarbonyl-2-oxapropyl)ethane (17a)** (13.4 g, 39.8% based on starting triol), b.p. 166 °C,  $\delta$  0.94 (s, 3 H, CMe), 3.39 (s, 6 H, neopentyl CH<sub>2</sub>), 3.65 (s, 9 H, OMe), and 4.00 (s, 6 H, OCH<sub>2</sub>CO) (Found: C, 50.05; H, 7.05. C<sub>14</sub>H<sub>24</sub>O<sub>6</sub> requires C, 50.0; H, 7.2%). Treatment of this ester (13.3 g) with refluxing aqueous sodium hydroxide (5.0 g in 50 cm<sup>3</sup>) for 3 h followed by distillation of the methanol, acidification with concentrated hydrochloric acid, evaporation to dryness *in vacuo*, and extraction of the residue with acetone gave (12b) (11.5 g) as a heavy yellow syrup which did not crystallise,  $\delta$ (CD<sub>3</sub>COCD<sub>3</sub>) 0.98 (s, 3 H, CMe), 3.57 (s, 6 H, neopentyl CH<sub>2</sub>), 4.18 (s, 6 H, OCH<sub>2</sub>CO), and 9.52 (br s, 3 H, CO<sub>2</sub>H).

**Tetrakis-(3-carboxy-2-oxapropyl)methane (12c).**—Reaction of a suspension of pentaerythritol (13.6 g, 0.100 mol) in 4 stages as before with sodium *t*-pentoxide and *NN*-dimethylchloroacetamide gave a dark gum (47 g). Preparative t.l.c. (ethanol–ethyl acetate, 1 : 3 v/v) of a sample (400 mg) of this gum gave as the most polar band, the tetra-amide (13c) (108 mg), which did not crystallise;  $\delta$  2.96 and 3.02 (each s, 24 H, N-Me), 3.63 (s, 8 H, neopentyl CH<sub>2</sub>), and 4.17 (s, 8 H, OCH<sub>2</sub>CO). Hydrolysis of the remainder of the dark gum as above gave crude syrupy acid (33.7 g) which was esterified as before giving crude methyl ester (28.1 g). A portion (1.25 g) of this material was subjected to preparative t.l.c. (acetone–toluene, 3 : 17 v/v) and gave as the major component **tetrakis-(3-methoxycarbonyl-2-oxapropyl)methane (17b)** (579 mg) which was distilled (sublimation block) at 0.005 mmHg (200–220 °C);  $\delta$  3.65 (s, 8 H, neopentyl CH<sub>2</sub>), 3.73 (s, 12 H, OMe), and 4.12 (s, 8 H, OCH<sub>2</sub>CO) (Found: C, 47.85; H, 6.8. C<sub>17</sub>H<sub>28</sub>O<sub>12</sub> requires C,

48.1; H, 6.65%). Hydrolysis of this pure ester (17b) (500 mg) with aqueous sodium hydroxide (207 mg in 10 cm<sup>3</sup>) at reflux followed by evaporation of the methanol, percolation through an ion-exchange column (Amberlite IR 120, H<sup>+</sup> form), and removal of the water *in vacuo* gave the tetra-acid (12c) as a gum (465 mg) which did not crystallise;  $\delta$ (CD<sub>3</sub>COCD<sub>3</sub>) 3.72 (s, 8 H, neopentyl CH<sub>2</sub>), 4.18 (s, 8 H, OCH<sub>2</sub>CO), and 8.94 (br s, 4 H, CO<sub>2</sub>H).

**Reactions of  $\alpha$ -Halogenoacetic Acid Esters with 2,2-Dimethylpropane-1,3-diol in the Presence of Sodium *t*-Pentoxide.**—Reaction of 2,2-dimethylpropane-1,3-diol in two steps (see above) with sodium *t*-pentoxide (2 × 1.03 mol. equiv.) and the appropriate  $\alpha$ -halogeno-ester (2 × 1.03 mol. equiv.; methyl chloroacetate, ethyl bromoacetate, or *t*-butyl chloroacetate) and work-up as described for the related amide (13a) gave dark oils in the former two cases and a dark rubbery insoluble material from the *t*-butyl ester. <sup>1</sup>H N.m.r. spectra of the two oils were very complex. Attempted distillation gave poor recoveries (ca. 20%) of distillable material which again gave complex <sup>1</sup>H n.m.r. spectra.

We thank the Natural Sciences and Engineering Research Council of Canada for an operating grant (to R. McC.).

[0/907 Received, 13th June, 1980]

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