Propentdyopents [5-(2-Oxo-2*H*-pyrrol-5-ylmethylene)pyrrol-2(5*H*)-ones] and Related Compounds. Part 1. On the Structure of the Propentdyopent–Alkanol Adducts

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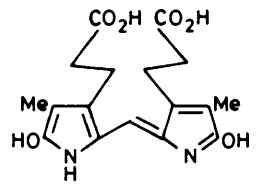
The history of the propentdyopent problem is briefly summarised. Tetraethyl(methanol)propentdyopent and tetraethyl(water)propentdyopent are prepared from octaethylhaemin and from 3,3′,4,4′-tetraethyl-2,2′-methylenedipyrrole-5,5′-dicarboxylic acid under specified oxidative conditions, are interconverted under appropriate acidic conditions, and readily form the orange zinc(II) complex of tetraethylpropentdyopent. Arguments are advanced to show that the water and methanol derivatives are to be formulated as the valley adducts (**18a**, **b**) of tetraethylpropentdyopent.

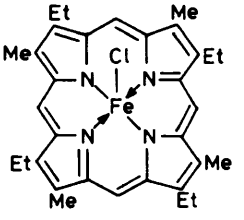
Two series of naturally occurring dipyrrolic systems which are derived from haem are known—the propentdyopents [5-(2-oxo-2*H*-pyrrol-5-ylmethylene)pyrrol-2(5*H*)-ones] and the bilifuscins and both are obscure and poorly defined in chemical terms. We propose in this and subsequent papers to bring the propentdyopents into the centre stage, leaving the bilifuscins till another time or to other hands.

The history of the propentdyopents is both long and confused.[1] The substances were first encountered in 1870 by Stokvis,[2] who found that they occurred in urine from jaundiced patients, and in pigment gallstones, and could be prepared by the chemical oxidation of bile pigments. The substances were characterised by a colour test (the Stokvis reaction) in which a red colour was produced on reduction in alkaline solution. The group was rediscovered in 1934 by Bingold[3] who introduced the pentdyopent nomenclature based, in a flamboyant deviation from the norm, on the absorption maximum (525 nm) of the red pigment formed in the Stokvis reaction. Much later, von Dobeneck[4] modified the nomenclature in such a way that the term pentdyopent refers to the pigment molecule of the colour test; its precursor (also coloured) is referred to as propentdyopent; while the latter system forms colourless adducts with certain nucleophiles (such as water and alcohols) which are referred to as, for example, methanol–propentdyopent adducts: it is the corresponding water adducts which appear to occur naturally. Bingold proposed that these substances arose from the catabolism of haem or bilirubin.[5] Although the results are not clear cut, there are some reports which point to the enzymatic generation of such substances,[6] and there is now clear evidence for a photocatabolic pathway from bilirubin.[7]

Following Bingold's observations, the problem of the chemical nature of the propentdyopents was taken up by Hans Fischer and his school at Munich, and in 1937 the first of a series of papers extending over 30 years was published.[8] Experiments with systems with propionic acid substituents led Fischer and Müller[8] to suggest that the propentdyopents were dihydroxypyrromethenes which were formulated as (**1**). Work with systems possessing propionic acid substituents was hampered however by excessive solubility in water, and subsequently Fischer and von Dobeneck turned to tetra-alkyl substituted compounds. Bingold[5] had earlier shown that oxidation of ammoniacal solutions of protohaemin with hydrogen peroxide gave a product with a positive Stokvis reaction, and Fischer and von Dobeneck[9] used this type of oxidative cleavage to obtain the diethyldimethyl propentdyopent system from aetiohaemin I (**2**), and the propentdyopent (adducts) were formulated as, for example, (**3**). Alternative preparations from pyrromethenes and dipyrrol-2-ylmethanes were also discovered.[9]



(**1**)



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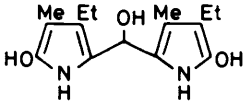

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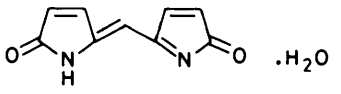
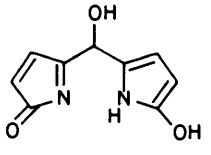
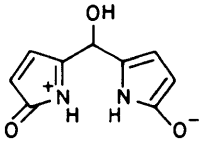


(**4**)

Subsequent studies[10,11] on a variety of synthetic propentdyopent adducts, and, particularly, on their metal complexes, showed that the system contained two hydrogen atoms less than indicated by a structure such as (**3**). The structure of the water–propentdyopent adducts was then summarised[11] by the general formulation (**4**) and the problem of structure became that of



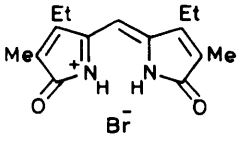
(**5**)



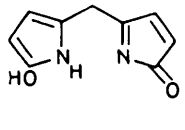
(**6**)

determining the position of the addition of the water molecule. Partly on the analogy with triphenylmethane pigments, the carbinol formula (**5**) was adopted, with the reservation that a betaine form (**6**) was also possible. In the case of the 3,3′-diethyl-4,4′-dimethyl system the propentdyopent was isolated as the hydrobromide (**7**) in the form of deep red needles.

In 1962, and working now with the tetramethyl system, von Dobeneck[12] returned to the problem of examining the dihydroxypyrromethenes, which he formulated as being based on

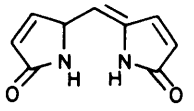


(**7**)

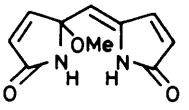


(**8**)

the skeleton (**8**). However, subsequent structural revisions[13,14] led to the adoption of structure (**9**) for this skeleton, and with this revision von Dobeneck returned to structure (**10**), which had previously been considered but rejected,[15] as a general representation for the methanol–propentdyopent adducts. In so doing he referred to some of the evidence now to be presented, and which has been communicated briefly.[16]



(**9**)

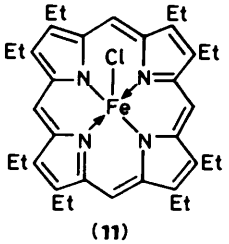


(**10**)

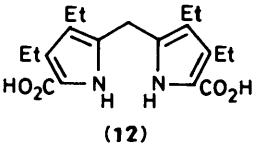
In making a fresh approach to the propentdyopent series, we decided to use the tetraethyl substitution pattern, partly because this had not been employed before, and partly because octaethylporphyrin, one of the possible precursors, is much more convenient to manipulate than is octamethylporphyrin.[17] In this preliminary study, we restricted ourselves to water and to methanol adducts.

The propentdyopent adducts were prepared in three ways. (i) By treatment of octaethylhaemin (**11**) with hydrogen peroxide in the presence of sodium methoxide at −10 °C. This procedure generally gave a mixture of methanol and water adducts, but by suitable experimental work-up it could be arranged that the water adduct was the main product, albeit in low isolated yield (10%). The water adduct had an analysis consistent with its formulation as $C_{17}H_{24}N_2O_3$. The substance was identical with that prepared from dipyrrolic precursors (below): this appears to be the first time that this important identity has been established.

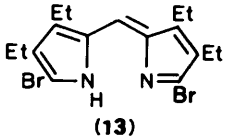
(ii) From 3,3′,4,4′-tetraethyl-2,2′-methylenedipyrrole-5,5′-dicarboxylic acid (**12**)[18,*] by oxidation with lead(IV) acetate to give the water adduct in 13% yield. In an alternative oxidation procedure, which is reported to work well (60% yield) with the tetramethyl analogue,[19] the diacid (**12**) was treated with 4 mol equiv. of bromine in methanol at −65 °C. The methanol–propentdyopent adduct was isolable in low but variable amount (maximum 18%) and the 5,5-dibromopyrromethene (**13**) was always obtained as a by-product. In spite of the unsatisfactory nature of this preparation of the methanol adduct, it was employed routinely because of the ready availability of the starting material (**12**). The tetraethyl(methanol)propentdyopent adduct had an analysis consistent with its formulation as $C_{18}H_{26}N_2O_3$ and was shown to be monomeric by osmometry.



(**11**)

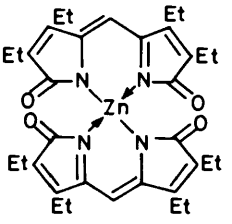


(**12**)

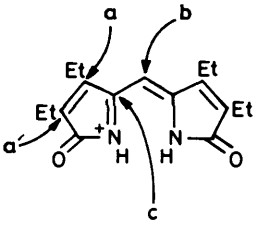


(**13**)

(iii) Treatment of either the water or the methanol adducts with zinc(II) acetate in methanol gave the zinc(II) complex (**14**), the structure of which was established by elemental analysis, n.m.r. spectroscopy, and literature precedent.[11] Treatment of the zinc(II) complex under acidic conditions with methanol gave the methanol adduct; and with water the water adduct was obtained. Analogously the water and methanol adducts could be interconverted under acidic conditions by treatment with an excess of the other nucleophile *via* the protonated tetraethylpropentdyopent cation [(**15**) $\lambda_{max.}$ 410 nm] formed by acid-catalysed elimination of water or methanol, respectively.

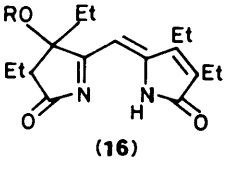


(**14**)

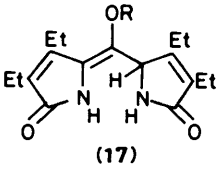


(**15**)

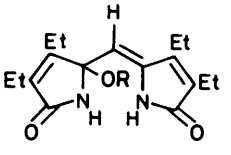
The solution to the alkanol–propentdyopent structural problem thus rested on determining the position of addition of the nucleophilic solvent (water, methanol) to the cation (**15**) or to the corresponding free base. Such addition was conceivable (i) at a β position [a,a′ in (**15**)] to give a β-adduct such as (**16**); (ii) at the *meso*-bridge [b in (**15**)] to give the *meso*-derivative (**17**) or tautomer; and (iii) at the valley position [c in (**15**)] to give the adduct (**18**) or a tautomer.



(**16**)



(**17**)



(**18**) R = H
R = Me

Structure (**16**) was ruled out by the n.m.r. evidence: two exchangeable NH protons were present in the methanol adduct, and all of the methylene groups (multiplet at *ca.* δ 2.3) were attached to unsaturated carbon. Distinguishing between (**17**) and (**18**) proved to be more difficult. However the available evidence clearly favoured (**18**). Thus treatment of the water adduct with diazomethane in tetrahydrofuran for 24 h did not generate the methanol adduct. This argues against structure (**17**; R = H) for the water adduct, since this structure contains a vinylogous carbamic acid system which would be expected to be appreciably acidic, and to be susceptible to methylation with diazomethane.

On the basis of chemical shift, the signal at δ 4.7 did not distinguish securely between [(**17**) valley H] and [(**18**) *meso*-H]. However, the fact that this signal was a singlet, and did not appear to be appreciably coupled to either NH (double irradiation at −30 °C) favoured (**18**) over (**17**).

The determining argument came from a deuteriation experiment. Treatment of zinc(II) bis(tetraethylpropentdyopent) (**14**) with MeOD containing a trace of CF_3CO_2D gave a deuteriated tetraethyl(methanol)propentdyopent adduct. N.m.r. spectroscopy showed that the two imino functions had been deuteriated,

* Such compounds have also been named as substituted dipyrrol-2-ylmethanes.

but the signal at δ 4.7 still corresponded to one proton. Process b → (**17**) necessarily results in the introduction of a deuterium into the valley position, whereas process c → (**18**) does not necessarily lead to *meso*-deuteriation. It is, therefore, concluded that the latter process has occurred, and that the water adduct is to be formulated at (**18a**), and the methanol adduct as (**18b**). The formation of the valley adducts (**18**) thus finds analogy in the attack of nucleophiles on the 5-methylenepyrrol-2(5*H*)-one system[20] and on the 5-methylenepyrrolidin-2-one system.[21]

The preparative methods described above, while of considerable interest mechanistically,[22] gave disappointingly low yields. Further progress had to await the discovery of a superior preparative method, which has now been achieved.[23]

Experimental

General.—Laboratory procedures and instrumental conditions were as previously described.[24] Light petroleum refers to that fraction b.p. 60—80 °C. Alumina was Hopkins and Williams CAMAG (Brockmann Activity Grade I) alkaline alumina, which was deactivated to the required grade by shaking 100 g of this material with the appropriate volume of water (*viz.* Grade II, 3 ml; Grade V, 15 ml). All columns were made up in light petroleum. Thin layer chromatography was on plates (20 cm × 20 cm × 0.25 mm) of Merck HF_{254} prepared in house and developed with 4% methanol in chloroform. The homogeneity of all products was checked by t.l.c.

Diethyl 3,3′,4,4′-Tetraethyl-2,2′-methylenedipyrrole-5,5′-dicarboxylate (with I.A.D. Gale). (a) A stirred solution of ethyl 3,4-dimethylpyrrole-2-carboxylate[25] (7.4 g) in carbon tetrachloride was treated dropwise with a solution of bromine (1.7 ml) in carbon tetrachloride (15 ml) over 10 min under u.v. irradiation (medium-pressure mercury lamp, 100 W). Irradiation and stirring were continued for a further 40 min. The solvent was removed and the dark red oil was refluxed for 1 h with methanol (65 ml) and 48% HBr (7.5 ml). The solution was kept at 0 °C overnight, and the crystalline solid was removed and recrystallised from aqueous methanol to give colourless needles (4.5 g, 64%) of the *title compound*, m.p. 97—99 °C (Found: C, 68.6; H, 8.7; N, 6.9. $C_{23}H_{34}N_2O_4$ requires C, 68.65; H, 8.5; N, 6.95%); $\lambda_{max.}$(EtOH) 277.5 infl. (26 300) and 292.5 nm (31 600); ν(Nujol) 3 340, 1 690, and 1 665 cm^{-1}; δ($CDCl_3$) 9.64 (br s, NH), 4.23 (q, OCH_2), 3.92 (s, *meso*-CH_2), 2.72, 2.42 (m of q, CH_2CH_3), and 1.25, 1.12, 1.05 (m of t, 6 × CH_3). The crystal structure of this substance was determined.[26]

(b) Ethyl 5-acetoxymethyl-3,4-diethylpyrrole-2-carboxylate[27] (6 g) was refluxed with 48% HBr (10 ml) in ethanol (100 ml) for 30 min after which the solution was cooled, diluted slowly with water, and scratched to induce crystallisation. The solution was kept in the cold and filtered to yield the title compound (4.2 g, 93%) as colourless needles, m.p. 95—100 °C.

3,3′,4,4′-Tetraethyl-2,2′-methylenedipyrrole-5,5′-dicarboxylic Acid (**12**).—The foregoing diester (1 g) was refluxed with 10% aqueous sodium hydroxide (3 ml) in ethanol (25 ml) for 24 h. The yellow solution was filtered, cooled in ice, and acidified to Congo Red with dilute sulphuric acid. Water was then added to the solution, with scratching, when a flocculent white precipitate formed. (On occasions an oil formed at this stage which could be rendered solid by tituration with light petroleum.) The white solid was filtered off, washed with water, and dried to yield the title compound (0.66 g, 77%) as an unstable, off-white solid, m.p. 152—159 °C (decomp.). This product could be used without further purification: extraction with benzene raised the m.p. to 181—182 °C (lit.,[18] m.p. 186 °C); $\nu_{max.}$(Nujol) 3 215 and 1 664 cm^{-1}.

Tetraethyl(water)propentdyopent [5-(3,4-*Diethyl*-5-*hydroxy*-2-*oxo*-2,5-*dihydropyrrol*-5-*ylmethylene*)-3,4-*diethylpyrrol*-2(5H)-*one*] (**18a**).—(a) *From octaethylhaemin* (**11**). Methanolic sodium methoxide [sodium (0.42 g) and methanol (40 ml)] was added with stirring to a solution of octaethylhaemin (210 mg) in chloroform (65 ml). The solution was cooled to −10 °C and an ice-cold solution of hydrogen peroxide (28%; 14 ml) in methanol (14 ml) was added to the stirred solution over 30 min. The mixture was stirred for a further 30 min at −10 °C after which it was treated with manganese dioxide and allowed to warm to room temperature. The mixture was filtered through Celite, and the filtrate was treated with water to cause phase separation. The aqueous layer was extracted twice with chloroform and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on Grade V alkaline alumina. Chloroform eluted a small amount of methanol propentdyopent adduct, while 10% methanol in chloroform eluted a major component which was recrystallised from chloroform–light petroleum to give tetraethyl(water)propentdyopent (21 mg, 10%) as a white powder, m.p. 169—172 °C (decomp.). Recrystallisation was wasteful but raised the melting point to 174—175 °C (decomp.) (Found: C, 66.55; H, 7.8; N, 8.9%; M^+, 304.180. $C_{17}H_{24}N_2O_3$ requires C, 67.1; H, 7.95; N, 9.2%; *M*, 304.179); $\lambda_{max.}$(EtOH) 280 nm (21 400); $\nu_{max.}$(Nujol) 3 280, 1 680, and 1 652 cm^{-1}; δ($CDCl_3$) 9.05, 7.48 (both br s, NH), 5.90 (br s, OH), 4.80 (s, *meso*-H), *ca.* 2.20 (m, CH_2), and *ca.* 1.1 (m, CH_3).

(b) *From the dicarboxylic acid* (**12**). The dicarboxylic acid (**12**) (106 mg) in acetic acid (20 ml) was treated under nitrogen with lead(IV) acetate (665 mg, 4.5 mol). The solution, which became deep red, was stirred for 24 h at room temperature. The resulting pale red solution was basified to pH 11 (2M-NaOH) and was then extracted continuously with ether (24 h). The pale pink extract was diluted with a little chloroform to dissolve the white solid which it contained, and the solution was dried ($MgSO_4$). The filtered solution was taken to dryness and treated with chloroform–light petroleum to give, after some hours at 0 °C, tetraethyl(water)propentdyopent (11.5 mg, 13%) as a white solid, m.p. 165—168 °C, identical (mixed m.p., i.r., t.l.c.) with the above (Found: C, 66.9; H, 7.8; N, 9.05%).

(c) *From tetraethyl(methanol)propentdyopent* (**18b**). The methanol adduct (10 mg) was dissolved in 10M-hydrochloric acid (1.5 ml) and then diluted with water (20 ml). The solution was neutralised (Congo Red) with 10% aqueous sodium hydroxide, and extracted thrice with chloroform. The extract was dried ($MgSO_4$), filtered, concentrated and diluted with light petroleum to give the water adduct (5 mg, 52%) as a white solid m.p. 164—167 °C (decomp.) (mixed m.p. water adduct 173—175 °C (decomp.); mixed m.p. methanol adduct 143—151 °C (decomp.).

Reactions of the Water Adduct.—(a) *Diazomethane.* Treatment of the water adduct with diazomethane in tetrahydrofuran for 92 h failed to produce a detectable amount of the methanol adduct (t.l.c.) and the starting material was isolated (50% recovery).

(b) *Treatment with trifluoroacetic acid–deuterium oxide.* The water adduct (20 mg) dissolved in trifluoroacetic acid (0.3 ml) to give a yellow solution ($\lambda_{max.}$ 410 nm). Dilution with deuterium oxide (2 ml) gave an oily yellow precipitate which solidified on basification to pH 12 (NaOD) to give the deuteriated water adduct (13 mg). A further 2.5 mg was obtained by chloroform extraction of the solution. The combined product was crystallised from chloroform–petroleum to give the (partially) O/N deuteriated adduct; ν($CHCl_3$) 3 570, 3 430, 3 250, 2 660, 2 560, 2 460, 1 690, and 1 665 cm^{-1}; ν(Nujol) 3 310, 3 250, 2 450, 1 680, 1 660, 1 193, and 700 cm^{-1}; δ 4.81 (s, 1 H; not exchangeable on shaking with D_2O).

(c) Zinc complex formation from the water adduct: see below.

Tetraethyl(methanol)propentdyopent. [5-(3,4-*Diethyl*-5-*methoxy*-2-*oxo*-2,5-*dihydropyrrol*-5-*ylmethylene*)-3,4-*diethylpyrrol*-2(5H)-*one*] (**18b**).—(a) *From the dicarboxylic acid* (**12**). The reaction gives low and irreproducible yields. The dicarboxylic acid (**12**) (500 mg) was pulverised and treated in cold methanol (3 ml) with a solution of bromine (0.3 ml) in methanol (3 ml) at 65 °C. The solution was stirred at −65 °C for 10 min, and then at room temperature for 25 h. The precipitate of the 5,5′-dibromopyrromethene (**13**) as its dihydrobromide [m.p. 209 °C (decomp.) (lit.,[18] 206 °C (decomp.)] was filtered off and crystallised from methanol–water to give 5,5′-dibromo-3,3′,4,4′-tetraethylpyrromethene (free base) as bright orange needles (29%), m.p. 164—166 °C) (Found: C, 49.6; H, 5.75; N, 6.6. $C_{17}H_{22}Br_2N_2$ requires C, 49.3; H, 5.35; N, 6.75%); δ($CDCl_3$) 10.15 (br s, NH), 6.61 (s, *meso*-H), 2.58, 2.40 (m, overlapping q, CH_2CH_3), and 1.28 and 1.21 (t, t-CH_2CH_3).

The filtrate from the foregoing dihydrobromide precipitation was taken to dryness and chromatographed in chloroform on alumina (Grade II, alkaline). The main brownish band, which gave a strong Stokvis reaction, was concentrated, and diluted with light petroleum to give the tetraethyl(methanol)propentdyopent as a white amorphous solid (best yield 18%). Crystallisation from methanol–water gave white needles, m.p. 166—168 °C (decomp.) (Found: C, 68.15; H, 8.45; N, 9.05%; M^+, 318.193. $C_{18}H_{26}N_2O_3$ requires C, 67.9; H, 8.25; N, 8.8%; *M*, 318.194); *M* (by osmometry in toluene), 306; $\lambda_{max.}$(EtOH) 279.5 nm (32 300); $\nu_{max.}$(Nujol) 3 360, 3 230br, 1 698, 1 660, 1 110, and 1 065 cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 440, 3 350br, 1 695, 1 105, and 1 045 cm^{-1}; the broad peak at 3 350 cm^{-1} disappeared on dilution; δ($CDCl_3$) 8.29 (br, NH), 6.12 (br, NH), 4.70 (s, *meso*-H), 3.12 (s, OMe), 2.21, 2.19 (m, CH_2CH_3), and 1.11 and 1.08 (m, CH_2CH_3), The broad lowfield singlets were concentration dependent, and exchangeable with D_2O.

Further elution of the column with methanol gave tetraethyl(water)propentdyopent, usually in trace amount.

(b) *From tetraethyl(water)propentdyopent.* (i) When tetraethyl(water)propentdyopent was refluxed with sodium methoxide alone, the solution was red at reflux, but decolourised on cooling. The methanol adduct could not be isolated but t.l.c. showed that a mixture of unknown products had been formed.

(ii) The water adduct (10 mg) was refluxed for 1 h with anhydrous trifluoroacetic acid (0.05 ml) in dry methanol (10 ml). The cooled solution was basified (dry Et_3N, 0.2 ml) and taken to dryness under reduced pressure. Chromatography on Grade V alkaline alumina with chloroform gave the methanol adduct (9.5 mg, 90%), m.p. 162—165 °C (decomp.). When this reaction was carried out in the absence of trifluoroacetic acid, the methanol adduct was still formed but in lower yield (52%).

(c) *From the zinc*(II) *complex* (**14**). Zinc(II) bis(tetraethylpropentdyopent) (20 mg) was suspended in CH_3OD (1 ml) and a trace of CF_3CO_2D was added to the stirred mixture. The solution was stirred with occasional warming on a water-bath for 20 min, during which time the zinc complex dissolved and the solution became pink. Addition of deuteriated water gave a pink solid which was quickly filtered off, washed with D_2O, and dried *in vacuo* to give deuteriated tetraethyl(methanol)propentdyopent (18 mg, 90%) indistinguishable (i.r., t.l.c.) from the deuteriated sample obtained by shaking the methanol adduct with D_2O (see below); δ($CDCl_3$) peaks at δ8.29 and 6.12 absent: *meso*-H at δ4.75 (s).

Reactions of the Methanol Adduct.—(a) *Zinc*(II) *complex of tetraethylpropentdyopent* (**14**). The methanol adduct (25 mg) was refluxed for 5 min with an excess of methanolic zinc acetate solution. The resulting orange solution, which already contained some crystals, was diluted with a few drops of water. The orange solid was filtered off, washed with water, and dried *in vacuo* to yield zinc(II) bis(tetraethylpropentdyopent) (22 mg, 88%) which crystallised from chloroform–light petroleum as orange, hair-like needles, m.p. >360 °C (colour change to dark brown at 290 °C) [Found: C, 64.25; H, 6.9; N, 8.55; Zn, 10.35 (from residue as ZnO). $C_{34}H_{42}N_4O_4Zn$ requires C, 64.2; H, 6.65; N, 8.8; Zn, 10.3%]; $\lambda_{max.}$($CHCl_3$) 362 (32 000). 372infl., (30 600), 493 (34 000), and 525 nm (29 000); $\nu_{max.}$(Nujol) 1 700 and 1 540 cm^{-1}; δ($CDCl_3$) 5.42 (s, *meso*-H), 2.45, 2.29 (qq, CH_2CH_3), and 1.19 and 1.06 (t, t, CH_2CH_3).

The zinc complex was also prepared from the water adduct using this procedure.

(b) *Deuteriation* The methanol adduct in ^1H chloroform was shaken at room temperature with D_2O, and the n.m.r. spectrum was recorded at intervals. The broad lowfield signals (δ8.29, 6.12) diminished at about equal rates, and after 130 min had vanished. The solvent was removed, and the residue was dissolved in CH_3OD and treated with D_2O to give white needles of [$^2H_2$]tetraethyl(methanol)propentdyopent, m.p. 168—172 °C (decomp.); M^+, 320 ($C_{18}{}^1H_{24}{}^2H_2N_2O_3$ requires *M*, 320); $\nu_{max.}$ 2 580 and 2 480 cm^{-1}.

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