Chemistry of Adamantane. Part IX.[1] 1,2-Difunctional Adamantanes; Synthesis and Reactions of Protoadamantane-4-spiro-oxiran

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The synthesis of protoadamantane-4-spiro-oxiran {octahydrospiro[2,5-methano-1H-indene-7,2′-oxiran]} and its isomerisation to protoadamantane-4-carbaldehyde are described. Electrophilic cleavage of the oxiran ring with simultaneous rearrangement gives 1,2-difunctional adamantane derivatives. Reactions of lithium carbenoids, from benzylidyne chloride and benzylidene bromide, with protoadamantan-4-one mainly lead to protoadamantan-4-yl phenyl ketone. 4-Phenylprotoadamantan-4-ols on treatment with acid preferentially undergo elimination to give 4-phenylprotoadamantene.

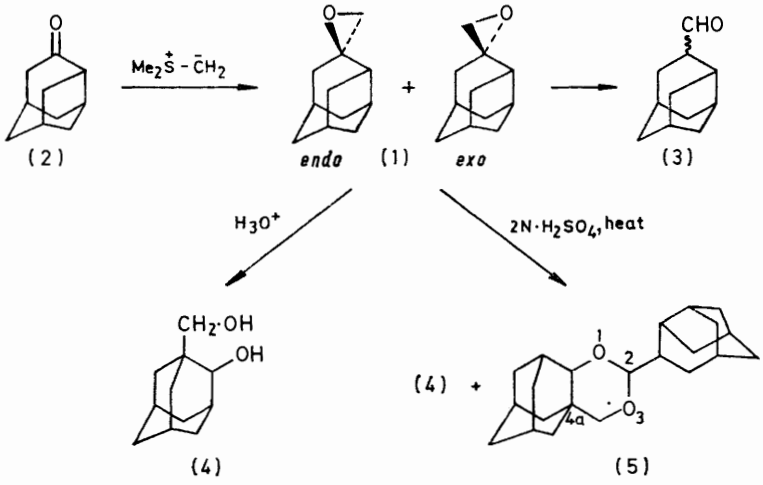
THE recent discovery [2] of certain 1,2-disubstituted adamantane derivatives possessing anti-depressant and anti-Parkinson properties encouraged us to explore convenient methods for the synthesis of ω-(2-substituted 1-adamantyl)alkylamines. We have previously described the preparation of such adamantylethyl and higher alkyl derivatives by intramolecular insertion reactions.[2,3] Such a process cannot be used to prepare 2-substituted adamantane derivatives with a functionalised methyl group at position 1 owing to steric factors. However, we have previously obtained 2-substituted 1-adamantylmethylamines by Hofmann degradation of the corresponding acetamides.[3a] Recently we have

[1] Part VIII, J. K. Chakrabarti, T. M. Hotten and D. E. Tupper, *Tetrahedron Letters*, 1975, 2241.

[2] J. K. Chakrabarti, M. J. Foulis, T. M. Hotten, S. S. Szinai, and A. Todd, *J. Medicin. Chem.*, 1974, **17**, 602.

[3] (*a*) J. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc.* (*C*) 1970, 1303; (*b*) W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, *ibid.*, 1968, 1657.

developed a direct and convenient route to these compounds. We have reported [1] the synthesis of protoadamantane-4-spiro-oxiran (1), and its various reactions leading to 2-substituted 1-adamantylmethyl derivatives. The present paper is concerned with the reaction conditions governing the exclusive formation of this oxiran, its isomerisation to the corresponding protoadamantane-4-carbaldehyde, and its cleavage and rearrangement to 1,2-difunctional adamantanes (based on the known rearrangement of the protoadamantane ring



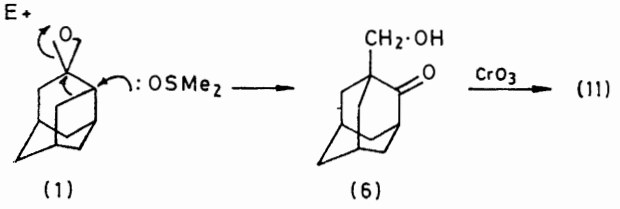
SCHEME 1

system to the thermodynamically more stable adamantane nucleus [4]). Reactions of lithium carbenoids derived from benzylidyne chloride and benzylidene bromide with protoadamantan-4-one are described. Attempts to rearrange 4-hydroxyprotoadamantane-4-carbonitrile and 4-phenylprotoadamantan-4-ol are also reported.

The oxiran (1) was obtained as a mixture of epimers (*endo* : *exo* 2 : 3) from the readily available protoadamantan-4-one (2). The 90 MHz n.m.r. spectrum (solvent $CDCl_3$) showed a singlet at δ 2.68 and a double doublet at 2.60 (*J ca.* 5.0 Hz) due to the oxiran methylene protons of the two isomers. Molecular models revealed that the oxygen atom in the *endo*-form is less sterically crowded and the methylene protons are in a near symmetrical environment. Thus the singlet is derived from the *endo*-isomer. On addition of the shift reagent $Eu(fod)_3$, the methylene signal of the *endo*-isomer, which can coordinate with the shift reagent more effectively, moves downfield faster than that of the *exo*-isomer.

The reaction of protoadamantan-4-one (2) with dimethylsulphonium methylide proceeds smoothly at *ca.* 54 °C (optimum temperature) to give essentially a quantitative yield of the oxiran (1). At lower temperatures the reaction is not complete and at higher temperatures the yield is low owing to the formation of 1-hydroxymethyladamantan-2-one (6) (10—30%). An electrophile (E^+) like $[Me_2S{\cdot}OMe]^+$, generated from trimethylsulphonium iodide and dimethyl sulphoxide at higher temperatures, could bring about concerted opening of the oxiran ring leading to the oxidation product (6) (Scheme 2). The ketone (6) forms an oxime and gives 2-oxoadamantane-1-carboxylic acid [5] (11) on oxidation with chromic acid.

The oxiran (1) reacts readily with acids. With catalytic amounts of mineral acids in aqueous dioxan it underwent ring opening and smooth rearrangement to give 2-hydroxy-1-adamantylmethanol (4). Protonation of the oxiran oxygen causes a sequence of reactions leading to selective cleavage of the C–O bond involving the more



SCHEME 2

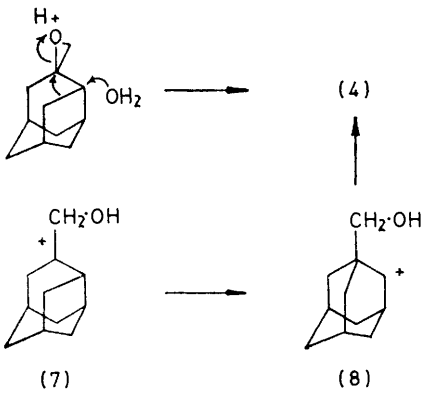
highly substituted carbon atom (Markownikoff). The simultaneous shift of the 2,3-bond in the protoadamantane 4-cation (7) is facilitated by the cation-stabilising effect of the geminal hydroxymethyl group. Addition of the available nucleophile to the adamantane 2-cation (8) gives the product (4). Alternatively, a nucleophilic addition to the protonated oxiran could occur in a concerted fashion, leading to the product as shown in Scheme 3.

The yield of the diol (4) decreased with increase in concentration of the acid and with increase in temperature, owing to the formation of by-products and polymeric material. For example, with 2N-sulphuric acid in boiling ethanol the oxiran (1) produced only 40—50% of

[4] D. Lenoir, R. Glaser, P. Mison, and P. von R. Schleyer, *J. Org. Chem.*, 1971, **36**, 1821; B. D. Cuddy, D. Grant, and M. A. McKervey, *Chem. Comm.*, 1971, 27.

[5] (*a*) J. A. Peters, J. D. Remijnnse, A. van der Wiele, and H. van Bekkum, *Tetrahedron Letters*, 1970, 3065; (*b*) I. Tabushi and Y. Aoyama, *J. Org. Chem.*, 1973, **38**, 3447.

the diol (4). Another product isolated (10—12%) was identified as 2-(protoadamantan-4-yl)adamantano[2,1-*d*][1,3]dioxan (5),* probably formed by the reaction of the

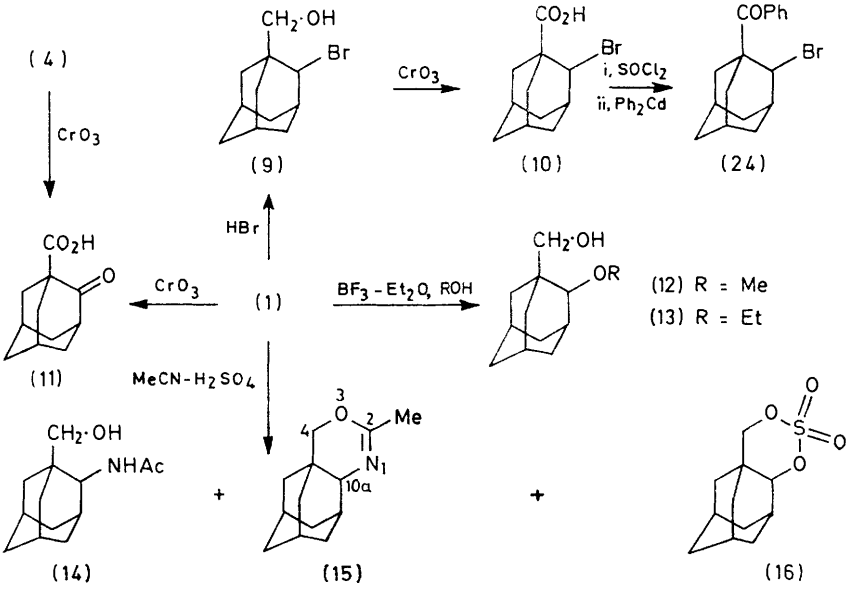


SCHEME 3

diol (4) with protoadamantane-4-carbaldehyde (3) derived from acid-catalysed isomerisation of the oxiran (1) (see later). The i.r. spectrum showed no hydroxy-absorption, and intense ether bands at 1 170—1 030 cm^{-1} were observed. The 90 MHz n.m.r. spectrum (solvent $CDCl_3$) revealed signals at δ 3.47 (>CH–O), 3.46 and 3.26 [non-equivalent CH_2 in an AB system (*J ca.* 9.5 Hz)], and 4.44 [doublet, O·CH·O coupled with a neighbouring proton (*J ca.* 6.5 Hz)]. The ^{13}C (22.63 MHz) chemical shifts and the peak multiplicities (off-resonance decoupling) support the above assignment (see Experimental section). The dioxan (5) was cleaved by concentrated sulphuric acid in acetic anhydride at room temperature. G.l.c.–mass spectrometric analysis of the product showed the presence of a major component (43%), identified as 2-hydroxy-1-adamantylmethyl acetate, and some 2-acetoxy-1-adamantylmethyl acetate (17%). No aldehyde component was identified. Alkaline hydrolysis of the acetates gave the diol (4).

In the presence of anhydrous hydrogen bromide, the oxiran (1) gave the rearrangement product 2-bromo-1-adamantylmethanol (9). The selectivity of the oxiran ring opening reactions coupled with the ready rearrangement makes this route attractive for the synthesis of various 1,2-difunctional adamantanes. These in turn can be easily converted into compounds otherwise only accessible by lengthy multi-stage syntheses. For example, the oxiran (1) or the diol (4) on oxidation with Jones reagent produced 2-oxoadamantane-1-carboxylic acid (11). Similar oxidation of the bromo-methanol (9) yielded the corresponding 2-bromoadamantane-1-carboxylic acid (10). A multi-step route to these acids has been reported.[5]

On treatment with boron trifluoride–ether complex in benzene,[6] the oxiran (1) isomerised to protoadamantane-4-carbaldehyde (3), which is remarkably stable, in contrast to the corresponding adamantane-1- and -2-carbaldehydes.[7] A similar isomerisation also occurred during attempted purification of the oxiran on silica gel.



SCHEME 4

Isomerisation in the presence of Sorbsil M60 in methylene chloride at room temperature for 72 h produced a mixture, shown by n.m.r. to contain 40% of the aldehyde (3), 40% of the starting oxiran, and 20% of another product (not characterised). The n.m.r. spectrum of the mixture (in CCl_4) revealed signals at δ 9.71 and 9.65 (1 : 3, respectively) due to the aldehyde protons of the two isomers. The signal from the methylene protons due to

* Compounds (5), (15), and (16) are more correctly designated by names of the type ' 2-methyldecahydro-4a,8: 6,10-dimethanocyclo-octa[*d*][1,3] oxazine '[for (15)], with which the numbering systems used agree.

[6] D. Farcasiu, *Synthesis*, 1972, 615.

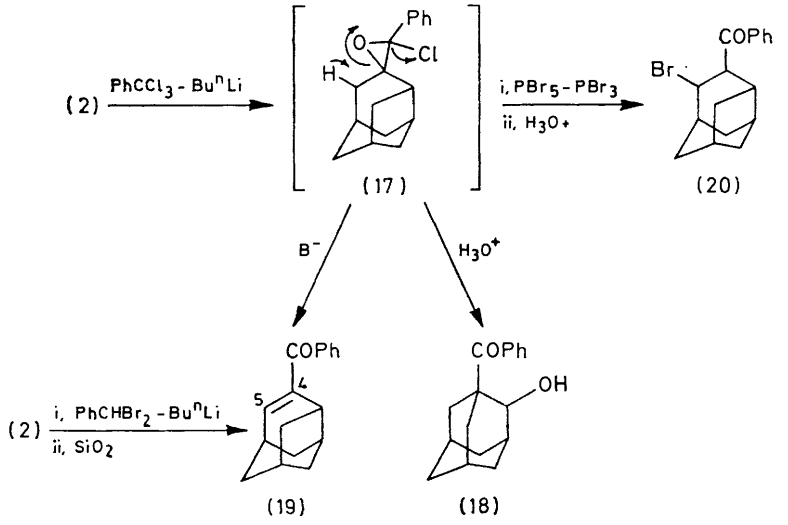
[7] (*a*) F. N. Stepanov, N. L. Dovgan, *Zhur. org. Khim.*, 1968, **4**, 277. (*b*) J. Scharp, H. Wynberg, and J. Strating, *Rec. Trav. chim.*, 1970, **89**, 18.

the *exo*-oxiran disappeared, whereas the singlet due to the *endo*-isomer remained more or less intact; the *exo*-isomer is the more prone to isomerisation. Further evidence of the structure of the aldehyde (3) is provided by the coupling constant (*J ca.* 4.0 Hz) of the aldehyde proton of the dinitrophenylhydrazone with the neighbouring H-4.

On treatment with boron trifluoride–ether complex in methanol, the oxiran (1) rearranged to 2-methoxy-1-adamantylmethanol (12). The ^{1}H n.m.r. spectrum (solvent CCl_4) exhibited a signal at δ 3.25 for H-2 (geminal to the methoxy-group), and an off-resonance doublet appears at δ 87.8 (>CH·OCH_3) in the ^{13}C n.m.r. spectrum. Similarly, the reaction in ethanol produced 2-ethoxy-1-adamantylmethanol (13), in high yield, also characterised as its acetate. The shift reagent Eu(fod)$_3$ revealed the magnetic nonequivalence of the CH_2·OH protons in the methoxy-alcohol (12) as in the cases of 2-hydroxy-1-adamantylmethanol (4) (see Experimental section) and 2-(2-hydroxy-1-adamantyl)ethanol.[8] However, the corresponding signal in the case of the ethoxy-alcohol (13) remained a singlet at all concentrations of the shift reagent.

The oxiran (1) underwent a Ritter reaction with acetonitrile and sulphuric acid to give a mixture of the rearrangement products *N*-(1-hydroxymethyl-2-adamantyl)acetamide (14) and 2-methyl-10a*H*-adamantano[2,1-*d*][1,3]oxazine (15), presumably formed by intramolecular quenching of a nitrilium intermediate. A small amount (*ca.* 1%) of the cyclic sulphate, adamantano-[2,1-*d*][1,3,2]dioxathian 2,2-dioxide (16) was also isolated by chromatography. This became the major product at higher temperatures (*ca.* 50 °C).

In view of our requirement for certain (2-substituted 1-adamantyl) phenyl ketones, we investigated the reaction of the lithium carbenoid generated from benzylidyne chloride and n-butyl-lithium [9] with protoadamantan-4-one, in the hope that the intermediate chloro-oxiran (17) would give the ketone (18) on treatment with acid as shown in Scheme 5. Treatment of the crude product with a catalytic amount of sulphuric acid in aqueous tetrahydrofuran produced only a small amount of the ketone (18). The main product isolated (18%) was protoadamant-4-en-4-yl phenyl ketone (19). The H-5 n.m.r. signal appeared as a pair of doublets centred at δ 6.92 ($J_{5,6}$ *ca.* 8.2, $J_{3,5}$ *ca.* 1.8 Hz). A base-catalysed



SCHEME 5

elimination reaction of the chloro-oxiran (17) may have occurred in a concerted manner as indicated. The crude product from the reaction of the carbenoid with protoadamantan-4-one, on treatment with phosphorus pentabromide–phosphorus tribromide, yielded 5-bromo-protoadamantan-4-yl phenyl ketone (20) after aqueous work-up. This could be derived by addition of HBr to protoadamant-4-en-4-yl phenyl ketone. However, 2-bromo-1-adamantyl phenyl ketone (24) was prepared by the reaction of the acid chloride of the acid (10) with diphenylcadmium.

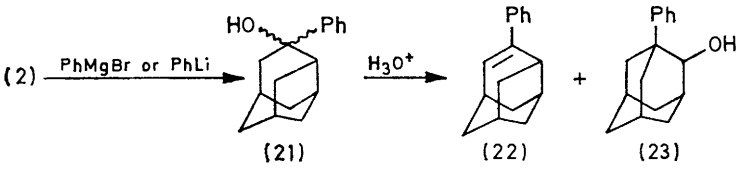
Since the chlorine attached to the postulated oxiran (17) seems to facilitate the elimination reaction, we examined the reaction of the carbenoid derived from benzylidene bromide and n-butyl-lithium [9b] with protoadamantan-4-one. The desired phenyloxiran could not be isolated, and only 20% of the elimination product (19) was isolated by chromatography. The reactive carbenoid appeared to have been generated by preferential abstraction of the benzylic proton during lithiation rather than by halogen–lithium exchange.[9b] The reaction of the ylide derived from dimethylbenzylsulphonium bromide and potassium t-butoxide [10] with protoadamantan-4-one did not result in 3′-phenylprotoadamantane-4-spiro-oxiran.

[8] A. F. Cockerill and D. M. Rackham, *Tetrahedron Letters*, 1970, 5153.

[9] (*a*) O. M. Nefedov, V. I. Shiryaev, *Zhur. obshchei. Khim.*, 1967, **37**, 1233; (*b*) G. Cainelli, N. Tangari, and A. U. Ronchi, *Tetrahedron*, 1972, **28**, 3009.

[10] M. J. Hatch, *J. Org. Chem.*, 1969, **34**, 2133.

The mixture of epimeric alcohols (21) obtained by addition of phenyl-lithium or phenylmagnesium bromide to protoadamantan-4-one, on attempted rearrangement with 5N-hydrochloric acid at room temperature, easily underwent dehydration leading to 4-phenylprotoadamant-4-ene (22) (Scheme 6). The n.m.r. spectrum showed a double doublet at δ 6.45 ($J_{5.6}$ *ca.* 7.5, $J_{5.3}$ *ca.* 1.8 Hz) for the olefinic proton. These values are similar to those reported [4] for the vinylic proton of 4-chloroprotoadamant-4-ene. The mass spectrum is similar to that of the parent alcohol (M^+ 210 = 228 − 18).



SCHEME 6

The alcohol mixture is extremely sensitive to elimination by acids. 4-Phenylprotoadamant-4-ene was also the main product of attempted separation of the epimers on silica gel. Elution with methylene chloride gave a small amount (*ca.* 5%) of the expected rearranged product, 1-phenyladamantan-2-ol (23). The elimination was also effected when (21) was heated with acetic anhydride.

Treatment of protoadamantan-4-one with potassium cyanide and sulphuric acid gave the cyanohydrin. No acid-catalysed rearrangement of the cyanohydrin could be effected. Prolonged treatment with 50% aqueous acid mainly caused disproportionation to protoadamantan-4-one.

EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. B.p.s were recorded from short-path distillation carried out with a Büchi Kugelröhr apparatus. Unless otherwise stated i.r. spectra were measured for potassium bromide discs with a Perkin-Elmer 457 instrument, ^{1}H n.m.r. spectra for solutions in deuteriochloroform (Me_4Si as internal reference) with a Varian A-60A spectrometer, and ^{13}C n.m.r. spectra (at 22.63 MHz under both broad-band and off-resonance continuous wave decoupling conditions) with a Bruker WH90 instrument. Mass spectra were obtained with an LKB-9000S spectrometer (ionising beam energy 20 eV). G.l.c. was conducted with a 1.2% SE30-GCQ column programmed from 150 to 250 °C. Unless mentioned otherwise the drying agent used was magnesium sulphate and column chromatography was carried out with Sorbsil M60 grade silica gel.

Protoadamantane-4-spiro-oxiran (1).—To a solution of protoadamantan-4-one [11] (15.1 g, 0.1 mol) and trimethylsulphonium iodide (31 g, 0.15 mol) in dry dimethyl sulphoxide (200 ml) was added potassium t-butoxide (14 g) under a stream of nitrogen (the outlet was connected to a trap containing chromic acid to destroy the dimethyl sulphide formed). The mixture was stirred at 50—55 °C for 18 h, cooled to *ca.* 10 °C and poured onto ice–water (200 ml). The product was extracted with carbon tetrachloride and the extract was washed with water, dried, and evaporated under vacuum to give an oil (16.3 g), which was distilled at 70—80 °C and 1.5 mmHg to yield a white waxy *solid* (12.8 g), m.p. 62—64°; $\nu_{max.}$ 3 020, 2 960—2 840, 1 290, 1 270, and 1 255 cm^{-1} (Found: C, 80.3; H, 9.7; O, 10.0. $C_{11}H_{16}O$ requires C, 80.4; H, 9.8; O, 9.7%).

The above experiment, when carried out at a higher temperature (80—90 °C), afforded a mixture of products. This was chromatographed (elution with methylene chloride) to produce only a small amount of the oxiran (1) (1%) and protoadamantane-4-carbaldehyde (3) (26%).

Subsequent elution with ethyl acetate gave 1-*hydroxymethyladamantan-2-one* (6) (33%), m.p. 91—97°, $\nu_{max.}$ ($CHCl_3$) 3 560 (OH) and 1 700 cm^{-1} (C=O), δ 3.33 (2 H, s, C*H*$_2$·OH), 2.92 (1 H, m, OH, exchanged in D_2O), and 1.13—2.48 (13 H, m, skeletal) (Found: C, 73.4; H, 9.2; O, 17.6. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95; O, 17.8%); *oxime*, m.p. 149—150° (from carbon tetrachloride) (Found: C, 67.5; H, 8.95; N, 6.9; O, 16.6. $C_{11}H_{18}NO_2$ requires C, 67.3; H, 9.25; N, 7.1; O, 16.3%).

2-*Hydroxy*-1-*adamantylmethanol* (4).—The oxiran (1) (7.0 g, 0.043 mol) was dissolved in dioxan (150 ml) and water (20 ml). The solution was cooled to *ca.* 10 °C and 10% aqueous sulphuric acid (2 ml) was added with stirring. The mixture was left at room temperature overnight. Most of the dioxan was removed slowly under vacuum at 50 °C and water was added to the residue simultaneously until crystallisation of the product was complete. The *crystals* were collected and dried at 50 °C under vacuum (yield 7.3 g), m.p. 172—174° (from di-isopropyl ether–n-hexane), $\nu_{max.}$ 3 400—3 100 cm^{-1}, δ (CCl_4) 3.77 (1 H, C*H*·OH), 3.28 (2 H, C*H*$_2$·OH), 4.2 (2 H, 2 O*H*, exchanged in D_2O), and 1.0—2.3 (13 H, m, skeletal). Addition of Eu(fod)$_3$ revealed the non-equivalence of the C*H*$_2$·OH protons, also observed in the related 2-(2-hydroxy-1-adamantyl)ethanol.[8] Europium induced shift gradients (relative to C*H*OH) were: 1.0 (C*H*OH), 0.98, 0.67 (C*H*$_2$OH), 0.92 (skeletal methylene proton at C-8 or C-9). The ^{13}C n.m.r. spectrum showed, δ 78.4 (d, *C*H·OH), 73.3 (t, *C*H$_2$·OH), 38.7, 37.6, 37.1, 36.2, 35.2, 33.1, 30.5, 27.7, and 27.7 (nine skeletal carbons). The mass spectrum showed *m/e* 180 (*M* − 2), 164 (*M* − 18), 157 (*M* − 31, CH_2OH), 146 (*M* − 36), 133, 93, and 91 (Found: C, 72.2; H, 9.67; O, 17.3. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95; O, 17.6%).

Reaction of Protoadamantane-4-spiro-oxiran with 2N-*Sulphuric Acid in Ethanol.*—The oxiran (1) (16.3 g) in ethanol (50 ml) and 2N-sulphuric acid (10 ml) was refluxed for 2 h. The solution overnight deposited a solid, which was filtered off and dried under vacuum at 60 °C. Crystallisation from methanol gave 2-(*protoadamantan-4-yl*)*adamantano*[2,1-d][1,3]*dioxan* (5) (3.6 g), m.p. 216—218°, $\nu_{max.}$ 2 940, 2 860, 1 460, 1 170, 1 140, 1 110, 1 095, 1 055, and 1 028

[11] W. H. W. Lunn, *J. Chem. Soc.* (*C*), 1970, 2124.

cm^{-1}, δ_H 3.47 (1 H, m, >CH·O·), 4.44 (d, ·O·CH·O, *J ca.* 6.5 Hz), 3.46 and 3.26 (2 H, non-equivalent CH_2, *J ca.* 9.5 Hz), and 1.1—2.6 (28 H, complex m, aliphatic), δ_C (C_6D_6) 106.3 (d, O·CH·O) 83.3 (d, >CH·O), 77.3 (t, CH_2·O), and 41.5—28.5 (skeletal), *m/e* 328 (M^+), 310 (M − 18), 193 (M − 135), 165, 164, and 147 (Found: C, 80.7; H, 9.6; O, 10.1. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8; O, 9.8%).

The mother liquor was evaporated to dryness (12.1 g). Elution from a column with 0—50% methanol in methylene chloride gave 2-hydroxy-1-adamantylmethanol (4) (7 g), m.p. 168—171° (from di-isopropyl ether–n-hexane).

Reaction of 2-(Protoadamantan-4-yl)adamantano[2,1-d]-[1,3]dioxan with Acetic Anhydride and Concentrated Sulphuric Acid.—A suspension of the adamantanodioxan (5) (0.1 g) in acetic anhydride (5 ml) was treated with concentrated sulphuric acid (2 drops) at room temperature. The solution was stirred for 6 h, poured onto a mixture of ice and 2N-sodium hydroxide, and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to an oil (0.08 g). The product was analysed by g.l.c.–mass spectrometry. The main component (43% by peak height), on the basis of its mass spectrum [*m/e* 223 (M^+ − 1), 206, (M − 18), 181 (M − 43, CH_3CO), 164 (M − 60), and 151 (M − 73, $CH_2O_2CCH_3$)] was identified as 2-hydroxy-1-adamantylmethyl acetate. The minor component (17% by peak height) showed *m/e* 264 (M^+ − 2), 222 (M − 44), 193 (M − 73, $CH_2O_2CCH_3$), 179, 162, 151, and 134, suggesting that it was 2-acetoxy-1-adamantylmethyl acetate.

A solution of the crude product from the above reaction in dioxan (5 ml) and 20% sodium hydroxide (5 ml) was refluxed for 2 h. The mixture was diluted with water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to an oil. Analysis of the product by g.l.c.–mass spectrometry showed the major component to be 2-hydroxy-1-adamantylmethanol (4).

Protoadamantane-4-carbaldehyde (3).—Boron trifluoride–ether complex (0.5 ml) was added to a solution of the oxiran (1) (0.1 g, 0.000 6 mol) in dry benzene (10 ml) in a separating funnel. The mixture was shaken, set aside for 2 min, washed with water, dried, and evaporated under vacuum to give a waxy solid (*ca.* 0.1 g), $\nu_{max.}$ 2 705 and 1 725 cm^{-1}, δ 9.81 and 9.73 (1 H, CHO), in the ratio 1 : 3 for the two epimers.

The oxiran (1) (1.0 g) and Sorbsil M60 silica gel (1.0 g) in dry methylene chloride (10 ml) were stirred at room temperature for 72 h. The silica gel was filtered off and washed with chloroform and the solvent was removed from the combined filtrate and washings to give an oil (0.8 g), $\nu_{max.}$ 2 705 and 1 725 cm^{-1} containing 40% of the aldehyde (3), δ (CCl_4) 9.71 and 9.65 (1 H, CHO, in the ratio 1 : 3), 40% unchanged oxiran (1), δ 2.68 (2 H, s, CH_2·O; *endo*-isomer), and 20% of an unidentified product. The oil was purified by column chromatography (elution with methylene chloride); distillation at 50 °C and 1 mmHg gave the *aldehyde*, $\nu_{max.}$ 2 705 and 1 725 cm^{-1} (Found: C, 80.2; H, 10.0; O, 9.9. $C_{11}H_{16}O$ requires C, 80.4; H, 9.8; O, 9.7%); *2,4-dinitrophenylhydrazone*, m.p. 181—183° (from ethanol), $\nu_{max.}$ 3 280, 1 510, and 1 330 cm^{-1}, δ 2.65—3.04 (1 H, m, H-4), 7.55 and 7.69 (2 d in the ratio 1 : 4 due to two forms of –CH=N *J ca.* 4 Hz), 7.92 (1 H, d, aryl H-6), 8.32 (1 H, dd, aryl H-5), 9.06 (1 H, d, aryl H-3), ($J_{3,5}$ 2.5, $J_{5,6}$ 9.8 Hz), 10.96 (1 H, s, NH), and 1.15—2.65 (14 H, m, skeletal) (Found: C, 59.4; H, 5.9; N, 16.2. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.85; N, 16.3%), *oxime*, m.p. 87—90° (from carbon tetrachloride–n-hexane), $\nu_{max.}$ 3 260 and 1 660 cm^{-1}, δ 7.45 and 7.50 (2 d in the ratio 1 : 9 due to two forms of –CH=N–, *J ca.* 5.5 Hz), 8.80 (1 H, s, N·OH, exchanged in D_2O), and 1.2—2.9 (15 H, m, skeletal) (Found: C, 73.9; H, 9.85; N, 7.9; O, 9.2. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.55; N, 7.8; O, 8.9%).

2-Bromo-1-adamantylmethanol (9).—To a cooled (*ca.* 10 °C) solution of the oxiran (1) (1.0 g, 0.006 mol) in glacial acetic acid (10 ml) was added 55% hydrogen bromide in acetic acid (10 ml). The mixture was stirred for 3 h at room temperature, diluted with water, and extracted with chloroform. The extract was washed with dilute sodium hydrogen carbonate solution and water, dried, and evaporated under vacuum to give an oil. Column chromatography (elution with methylene chloride) afforded the *product* (0.45 g, 30%), m.p. 138° (from n-hexane), $\nu_{max.}$ 3 500br 1 035, and 735 cm^{-1}, δ 4.65 (m, CHBr), 3.19 and 3.52 (2 H, CH_2·OH), and 1.0—2.5 (13 H, skeletal + 1 H, OH, exchanged with D_2O) (Found: C, 54.2; H, 7.1; Br, 32.4; O, 6.8; $C_{11}H_{17}BrO$ requires C, 53.9; H, 7.0; Br, 32.6; O, 6.5%).

2-Ethoxy-1-adamantylmethanol (13).—Boron trifluoride–ether complex (freshly distilled; 1 ml) was added under nitrogen to a solution of the oxiran (1) (0.48 g, 0.003 mol) in absolute ethanol (20 ml), cooled in ice. The mixture was stirred at room temperature for 2—3 h, then diluted with water, and the product was extracted into ether. The extract was washed with water, dried, and evaporated under vacuum to give an oil (0.5 g). Distillation at 120 °C and 1 mmHg gave an *oil* (0.4 g), $\nu_{max.}$ (neat) 3 400, 2 980—2 920, 1 100, 1 040, and 1 020 cm^{-1}, δ (CCl_4) 3.3—3.8 (3 H, m, CH·O·CH_2), 1.22 (3 H, t, CH_3), 3.18 (2 H, CH_2·OH), 2.83 (1 H, m, OH, exchanged in D_2O), and 1.0—2.4 (13 H, m, skeletal) [Eu(fod)$_3$-induced shift gradients: 1.0 (CHOEt), 2.10 (CH_2·OH), 1.64 (skeletal methylene proton at C-8 or C-9), 0.52 (OCH_2·CH_3), and 0.49 (OCH_2CH_3); the CH_2OH signal appeared as a singlet at all europium concentrations], *m/e* 210 (M^+), 192, 179, 164, and 135 (Found: C, 74.4; H, 10.5; O, 15.1. $C_{13}H_{22}O_2$ requires C, 74.3; H, 10.5; O, 15.2%). The alcohol (13) (0.1 g) was acetylated (acetic anhydride–pyridine) to give the *acetate* as an oil, which was distilled at 150 °C and 0.1—0.2 mmHg; $\nu_{max.}$ (neat) 1 745 cm^{-1}, δ (CCl_4) 3.23 (1 H, CH·OEt) 3.63 and 3.87 (non-equivalent CH_2, *J ca.* 10 ± 1 Hz), 3.25—3.55 (2 H, m, CH_2·O), 1.97 (3 H, s, Ac), 1.15 (3 H, t, CH_3), 1.1—2.1 (13 H, m, skeletal) [Eu(fod)$_3$ induced shift gradients: 1.0 (CHOC_2H_5), 2.95 (CH_2·O·CO), 0.87 (skeletal methylene proton at C-8 or C-9), 0.56 (OCH_2·CH_3), 0.22 (OCH_2·CH_3), and 3.00 (Ac)] (Found: C, 71.6; H, 9.8; O, 18.8. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6; O, 19.0%). A similar reaction of the oxiran in methanol gave *2-methoxy-1-adamantylmethanol* (12) as an oil, b.p. 130—135° at 0.1 mmHg, δ (CCl_4) 3.25 (1 H, CH·OMe), 3.17 (2 H, s, CH_2·OH), 3.30 (3 H, s, OMe), 2.40 (1 H, OH, exchanged in D_2O), and 1.0—2.4 (13 H, m, skeletal) [Eu(fod)$_3$ induced shift gradients: 1.0 (CH·OMe), 2.36 and 2.17 (CH_2·OH), 1.69 (skeletal methylene proton at C-8 or C-9), and 0.47 (OMe); the enhanced shifts for the hydroxymethylene protons indicate that co-ordination is favoured at this site rather than at the CH·OMe function], δ_C 87.8 (d, CH·OMe), 73.1 (t, CH_2·OH), 55.4 (q, OCH_3), and 39.0, 37.7, 37.3, 35.7, 33.6, 30.2, 29.1, 27.5, and 27.2 (nine skeletal carbons), *m/e* 196 (M^+), 178, 181, 165, and 135 (Found: C, 73.6; H, 10.25; O, 16.1. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.25; O, 16.3%).

Ritter Reaction of Protoadamantane-4-spiro-oxiran with

Acetonitrile.—The oxiran (1) (1.64 g, 0.01 mol) was added to a solution of concentrated sulphuric acid (15 ml) in acetonitrile (40 ml) at 5 °C. The mixture was stirred for 3 h at 25 °C, poured onto ice–water, and extracted with chloroform. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated to a waxy solid. This was chromatographed [elution with chloroform containing ethanol (0—20% v/v)] to give two fractions: (*a*) (0.02 g, 1%), *adamantano*[2,1-d][1,3,2]-*dioxathian 2,2-dioxide* (16), $\nu_{max.}$ 1 385 and 1 190 cm^{-1} (SO_2), δ 4.85 (1 H, CH·O), 3.92 and 4.40 (2 H, AB,d, CH_2·O, *J ca.* 11 Hz), and 0.5—2.8 (13 H, m, skeletal), *m/e* 244 (M^+), 164, and 146 (M − 98, H_2SO_4) (Found: C, 54.7; H, 6.5; O, 26.0; S, 13.2. $C_{11}H_{16}O_4S$ requires C, 54.2; H, 6.6; O, 26.2; S, 13.1%); and (*b*) (0.2 g), identified by n.m.r. as a mixture of 2-methyl-10a*H*-adamantano[2,1-*d*][1,3]oxazine (15) [δ 3.9 (1 H, –CH–N=), 2.95 (2 H, s, CH_2·O), 1.9 (3 H, s, Me), and 0.8—2.2 (13 H, m), *m/e* 205 (M^+) 163 (M − 42)] and *N*-(1-hydroxymethyl-2-adamantyl)acetanide (14) [δ 3.9 (1 H,CH·N), 2.80 and 3.17 (2 H, AB,d, CH_2, *J ca.* 11 Hz), *ca.* 4 (1 H, OH), and 0.8—2.2 (m, 13 H)]. Fractional shortpath distillation at 230 °C and 0.1 mmHg gave analytically pure *product* (14) (Found: C, 69.6; H, 9.25; N, 6.0. $C_{13}H_{21}NO_2$ requires C, 69.9; H, 9.5; N, 6.3%).

2-*Oxoadamantane*-1-*carboxylic Acid* (11).—To a stirred solution of 2-hydroxy-1-adamantylmethanol (4) (10.0 g, 0.055 mol) in reagent grade acetone (200 ml), Jones reagent [50 ml of a solution containing chromic oxide (13.4 g) and concentrated sulphuric acid (11.5 ml)] was added dropwise over 20 min. The mixture was stirred for 2 h and then methanol (50 ml) was added to destroy the excess of oxidant; the mixture was then diluted with water, and extracted with chloroform. The organic phase was washed with water, dried, and evaporated to a white semi-solid. Crystallisation from carbon tetrachloride gave the pure *product* (5.8 g), m.p. 167—169°, $\nu_{max.}$ 3 500—2 000, 1 715, and 1 695 cm^{-1}, δ 10.9 (1 H, CO_2H) and 1.8—2.8 (13 H, skeletal) (Found: C, 68.3; H, 7.45; O, 24.8. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25; O, 24.7%). The oxiran (1) (2.0 g), 0.012 mol) was similarly oxidised to give the oxo-acid (11) (1.4 g), as was 1-hydroxymethyladamantan-2-one (6).

2-*Bromoadamantane*-1-*carboxylic Acid* (10).—2-Bromo-1-adamantylmethanol (9) (2 g, 0.008 mol) was oxidised as above to give the acid (10) (2.06 g, 97%), m.p. 160°, δ 4.83 (1 H, CHBr), 9.55 (1 H, CO_2H), and 1.5—2.5 (13 H, skeletal) (Found: C, 50.6; H, 5.95; Br, 30.7; O, 12.5. $C_{11}H_{15}BrO_2$ requires C, 50.8; H, 6.2; Br, 30.7; O, 12.3%).

2-*Bromo*-1-*adamantyl Phenyl Ketone* (24).—2-Bromoadamantane-1-carboxylic acid (10) (2.92 g, 0.001 1 mol) was refluxed with thionyl chloride (8.6 ml) for 30 min. The excess of reagent was removed and the crude acid chloride [$\nu_{max.}$ (neat) 1 795 cm^{-1}] was dried (KOH), dissolved in dry benzene (20 ml), and added dropwise to a solution of diphenylcadmium [from phenyl-lithium (12 ml of 2M-solution in benzene–ether) and cadmium chloride (2.57 g) [12]. The mixture was refluxed for 35 min, cooled in ice, and hydrolysed with cold 20% sulphuric acid. The product was extracted with carbon tetrachloride; the extracts were washed with sodium hydrogen carbonate solution, dried, and evaporated to leave an oil which was crystallised from methanol to yield the *ketone* (24) (0.7 g, 25%), m.p. 57°, $\nu_{max.}$ (Nujol) 1 675 cm^{-1} (C=O), δ (CCl_4) 5.05 (1 H, m, CHBr), 7.48 (5 H, m, Ph), and 1.4—2.75 (13 H, m) (Found: C, 64.0; H, 5.85; Br, 25.2; O, 5.2. $C_{17}H_{19}BrO$ requires C, 63.7; H, 6.0; Br, 25.0; O, 5.0%).

Reaction of Protoadamantan-4-one with Benzylidyne Chloride and n-Butyl-lithium.—Protoadamantan-4-one (1.5 g, 0.01 mol) and benzylidyne chloride (2.85 ml, 0.02 mol) were stirred in dry tetrahydrofuran (25 ml) under nitrogen at −70 °C. To this a solution of *ca.* 1.4M-n-butyl-lithium in n-hexane (14.6 ml, 0.02 mol) in dry tetrahydrofuran (20 ml) was added slowly over 1 h. The solution was stirred at −70 °C for another 1 h, then evaporated under vacuum to leave an oil, which was partitioned between chloroform and water. The organic phase was dried and evaporated to an oil, which was dissolved in aqueous dioxan at 0 °C and made just acidic with 2N-sulphuric acid. The mixture was stirred overnight, diluted with water, and extracted with chloroform. The extract was washed with dilute sodium hydrogen carbonate solution and water, dried, and evaporated to an oil. Short-path distillation gave two fractions: (*a*) *protoadamant-4-en-4-yl phenyl ketone* (19), b.p. 100 °C at 1 mmHg (0.45 g, 20%), m.p. 73° (from n-hexane), $\nu_{max.}$ (neat) 1 650 cm^{-1} (C=O), δ (CCl_4) 6.92 (1 H, dd, H-5, $J_{3,5}$ *ca.* 1.8, $J_{5,6}$ *ca.* 8.2 Hz) (this allylic coupling was removed by irradiation at the frequency of H-3), 3.42 (1 H, m, H-3), 7.2—7.5 (3 H, m, aryl H), 7.5—7.7 (2 H, m, aryl H), and 0.8—2.8 (11 H, m, skeletal) (Found: C, 85.5; H, 7.85; O, 7.0. $C_{17}H_{18}O$ requires C, 85.7; H, 7.6; O, 6.7%); and (*b*) 2-hydroxy-1-adamantyl phenyl ketone (18), b.p. *ca.* 200 °C at 1 mmHg (0.05 g), 81% pure by g.l.c., *m/e* 256 (M^+), 238, and 135, δ (CCl_4) 4.18 (1 H, C*H*·OH), 3.35 (1 H, OH, exchanged in D_2O), 7.26—7.70 (5 H, m, Ph), and 1.2—2.5 (13 H, m, skeletal).

The crude product from a similar reaction of protoadamantan-4-one and benzylidyne chloride, as described above, was dissolved in phosphorus tribromide (5 ml) at 0 °C, phosphorus pentabromide (4.2 g, 0.01 mol) was added, and the mixture was stirred at room temperature overnight, poured onto ice, and extracted with carbon tetrachloride. The extract was washed with water, dried, and evaporated and the residue in carbon tetrachloride was chromatographed, (elution with n-hexane containing an increasing proportion of carbon tetrachloride). The major component was crystallised from methanol to give *5-bromoprotoadamantan-4-yl phenyl ketone* (20) (1.15 g, 37%), m.p. 90°, $\nu_{max.}$ 1 695 cm^{-1} (C=O), *m/e* 320/318 (M^+) and 239 (M − Br), δ (CCl_4) 3.92 (1 H, dd, H-4, $J_{4,5}$ *ca.* 9.0, $J_{3,4}$ *ca.* 1.5 Hz), 4.87 (1 H, dd, H-5, $J_{5,6}$ *ca.* 1.5 Hz), 7.3—7.6 (3 H, m, aryl H), 7.85—8.15 (2 H, m, aryl H), and 1.2—2.7 (12 H, m, skeletal) (Found: C, 63.7; H, 5.75; Br, 25.3. $C_{17}H_{19}BrO$ requires C, 64.0; H, 6.0; Br, 25.0%).

Reaction of Protoadamantan-4-one with Benzylidene Bromide and n-Butyl-lithium.—Protoadamantan-4-one (1.5 g, 0.01 mol) and benzylidene bromide (3.3 ml, 0.02 mol) were treated with n-butyl-lithium as described above. The mixture was stirred for 20 h, poured onto ice, and extracted with carbon tetrachloride. The extract was chromatographed (elution with methylene chloride) to give the olefin (19) (0.44 g, 19%).

4-Phenylprotoadamantan-4-ol (21).—To a solution of protoadamantan-4-one (1.5 g, 0.01 mol) in dry benzene (15 ml) was added dropwise, under nitrogen, a 2M-solution of phenyl-lithium (5 ml, 0.01 mol) in benzene–ether (7 : 3; 20 ml). The mixture was heated under reflux for 2 h, then cooled and 30% ammonium chloride solution (20 ml) was added. The organic phase was separated, washed with water, dried, and evaporated under vacuum to give an oil (2.3 g). Short-path distillation at 150 °C and 0.2 mmHg

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produced a waxy *solid* (2.0 g), $\nu_{max.}$ (neat) 3 400 cm^{-1} (OH), δ (CCl_4) 1.47 (1 H, s, OH exchanged with D_2O), 7.1—7.55 (5 H, m, Ph), and 1.1—2.85 (14 H, m, skeletal), *m/e* 228 (M^+), 210 (M − 18), 195, 168, 167, 155, 91, and 77 (Found: C, 83.9; H, 9.0; O, 6.9. $C_{16}H_{20}O$ requires C, 84.1; H, 8.85; O, 7.0%).

A similar yield of the same product was obtained when phenylmagnesium bromide was used. Separation of the mixture of *exo*- and *endo*-epimers by chromatography was attempted. Elution with methylene chloride produced two fractions: (i) (major) an oil (50%), distilled at 150 °C and 0.1 mmHg to give 4-*phenylprotoadamant*-4-*ene* (22), $\nu_{max.}$ (neat) 1 628 cm^{-1} (C=C), δ (CCl_4) 6.45 (1 H, dd, H-5), 3.10 (1 H, H-3) ($J_{5,6}$ *ca.* 7.5, $J_{5,3}$ *ca.* 1.8 Hz), 6.9—7.5 (5 H, m, Ph), and 1.1—2.7 (11 H, m) (Found: C, 91.1; H, 8.55. $C_{16}H_{18}$ requires C, 91.4; H, 8.65%); (ii) (minor) a wax (5%) characterised as 1-phenyladamantan-2-ol (23), $\nu_{max.}$ 3 400 cm^{-1} (OH), δ (CCl_4) 3.85 (1 H, m, C*H*·OH), 7.0—7.4 (5 H, m, Ph), and 1.0—2.7 [14 H, m, skeletal and OH (exchanged in D_2O)].

4-*Phenylprotoadamant*-4-*ene* (22).—A solution of 4-phenylprotoadamantan-4-ol (21) (2.1 g) in acetic anhydride (20 ml) was heated on a steam-bath for 8 h, poured onto ice, and extracted with diethyl ether. The extracts were washed with water, dried, and evaporated to an oil (1.6 g). Chromatography (elution with methylene chloride) gave the olefin (22) (0.9 g, 47%).

4-*Hydroxyprotoadamantane*-4-*carbonitrile*.—A solution of protoadamantan-4-one (7.8 g, 0.05 mol) in ethanol (50 ml) was stirred with a solution of potassium cyanide (5.1 g, 0.075 mol) in water (50 ml). The vessel was fitted with a nitrogen inlet, a dropping funnel, a pH electrode, and a gas outlet passing through alkaline iron(II) sulphate solution. Aqueous sulphuric acid (20 ml; containing 2.25 ml of conc. H_2SO_4) was added dropwise over 30 min with the temperature kept below 20 °C. The mixture was allowed to attain room temperature and stirred for 18 h. The pH was adjusted to 3.6 to destroy any residual hydrogen cyanide and the solution was purged with nitrogen. The ethanol was removed by vacuum distillation, and the residue diluted with water and extracted with chloroform. The extract was washed with water, dried, and evaporated to a yellow gum, which was chromatographed (elution with methylene chloride) to give unchanged protoadamantanone (0.6 g) and the *nitrile* (5.4 g, 59%), m.p. 149—151° (from n-hexane), $\nu_{max.}$ (Nujol) 3 400 (OH) and 2 240 cm^{-1} (C≡N), δ ($CDCl_3$–CCl_4) 1.2—2.9 (14 H, m, alkyl) and 3.7 (5, OH, exchanged with D_2O) (Found: C, 74.8; H, 8.8; N, 7.9; O, 8.9. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.55; N, 7.9; O, 9.0%).

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