

Microbiological Hydroxylation. Part 22.¹ Preparation of Some Bicyclic Substrates containing 15—16 Carbon Atoms

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From cyclododecanone a series of bicyclic alcohols and ketones containing 15—16 carbon atoms have been synthesised for use as substrates in microbiological hydroxylations.

MICROBIOLOGICAL hydroxylations of two monocyclic ketones, cyclododecanone and cyclopentadecanone, have been described recently.¹ Substitution was less selective and the formation of only one or two products is much less the rule than with steroid substrates. We decided to extend this work by examining the hydroxylation of bicyclic systems containing approximately the same number of carbon atoms as steroids and utilising cyclododecanone (10) as starting material.

Cyclododecanone (10) was converted into the β -oxo-ester (6),^{2,3} which reacted with methyl vinyl ketone to form (7) in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); triethylamine⁴ was ineffective as a catalyst. Acid-catalysed⁵ cyclisation, hydrolysis, and decarboxylation of (7) afforded (8), none of the isomeric compound (14) being formed. The oxo-ester (6) reacted smoothly with acrylonitrile, but acid-catalysed hydrolysis and decarboxylation of the adduct to form (5) was very slow. However compound (5) was obtained in good yield by using lithium iodide in collidine⁵ to hydrolyse the adduct. The oxo-group of the oxo-ester (4) did not react with ethyl bromoacetate and zinc (Reformatsky), a small quantity of compound (1) being isolated. In a model experiment the reaction of cyclododecanone with

lithium ethoxyacetylene was investigated. The desired adduct was obtained in very low yield, 77% of the ketone being recovered; so the reactions of (4) and (5) with lithium ethoxyacetylene were not studied.

The Cope reaction of compound (5) proceeded very slowly, only an 11% yield of the cyano-ester (2) being obtained, along with (3) formed by cyclisation of (5). The α -pyrone (9) reacts readily with dienophiles such as maleic anhydride and acetylenedicarboxylate.⁶ However compound (9) did not react with 2-chloroacrylonitrile,⁷ a reaction which would have afforded the phenol (15).

The desired compounds were finally obtained by Prelog's procedure from the β -oxo-aldehyde (11)⁸ and dimethyl acetonedicarboxylate, which yielded (12)⁸ as the major product accompanied by a small quantity of the α -pyrone (13). Hydrolysis and decarboxylation of (12) gave (15),⁸ and Birch reduction of the methyl ether of (15) followed by hydrolysis of the enol ether so formed yielded the $\alpha\beta$ -unsaturated ketone (14) accompanied by the fully substituted $\beta\gamma$ -isomer. After this stage of the work had been completed it was reported^{9,10} that base-catalysed cyclisation of the adduct obtained from

⁵ F. Elsinger, *Org. Synth.*, 1965, **45**, 7.

⁶ G. Markl and R. Fuchs, *Tetrahedron Letters*, 1972, 4691, 4695.

⁷ E. J. Corey, U. Koelliker, and J. Neuffer, *J. Amer. Chem. Soc.*, 1971, **93**, 1489.

⁸ V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, 1947, **30**, 1883.

⁹ V. Dave and J. S. Whitehurst, *J.C.S. Perkin I*, 1973, 393.

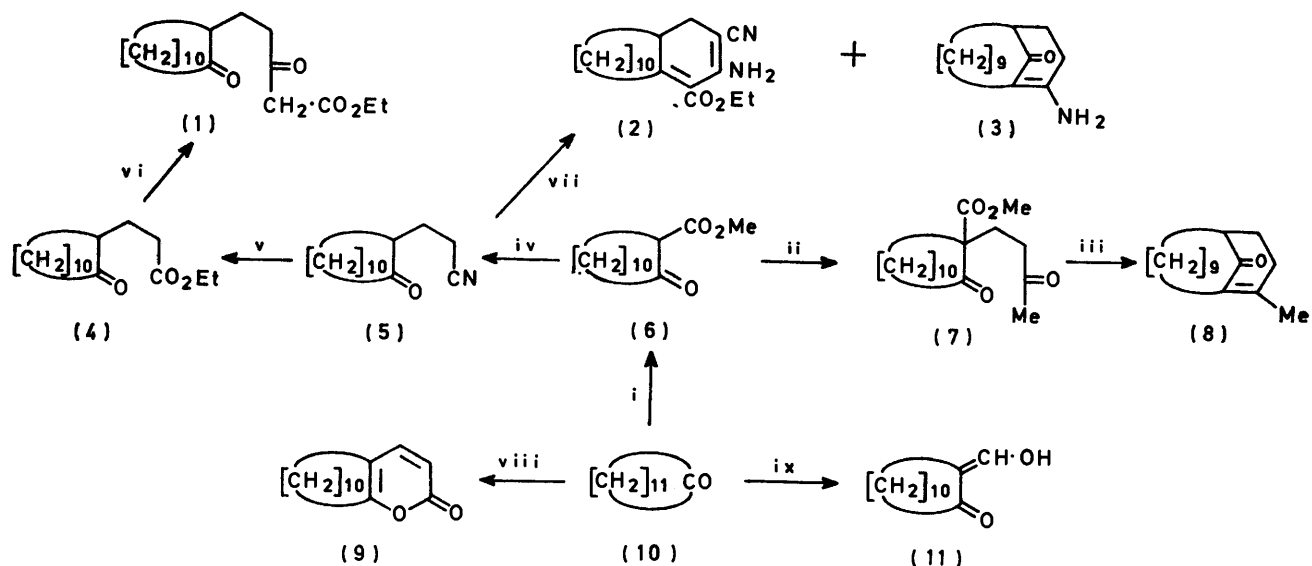
¹⁰ B. A. McAndrew and S. W. Russell, *J.C.S. Perkin I*, 1975, 1172.

¹ Part 21, M. J. Ashton, A. S. Bailey, and E. R. H. Jones, *J.C.S. Perkin I*, 1974, 1665.

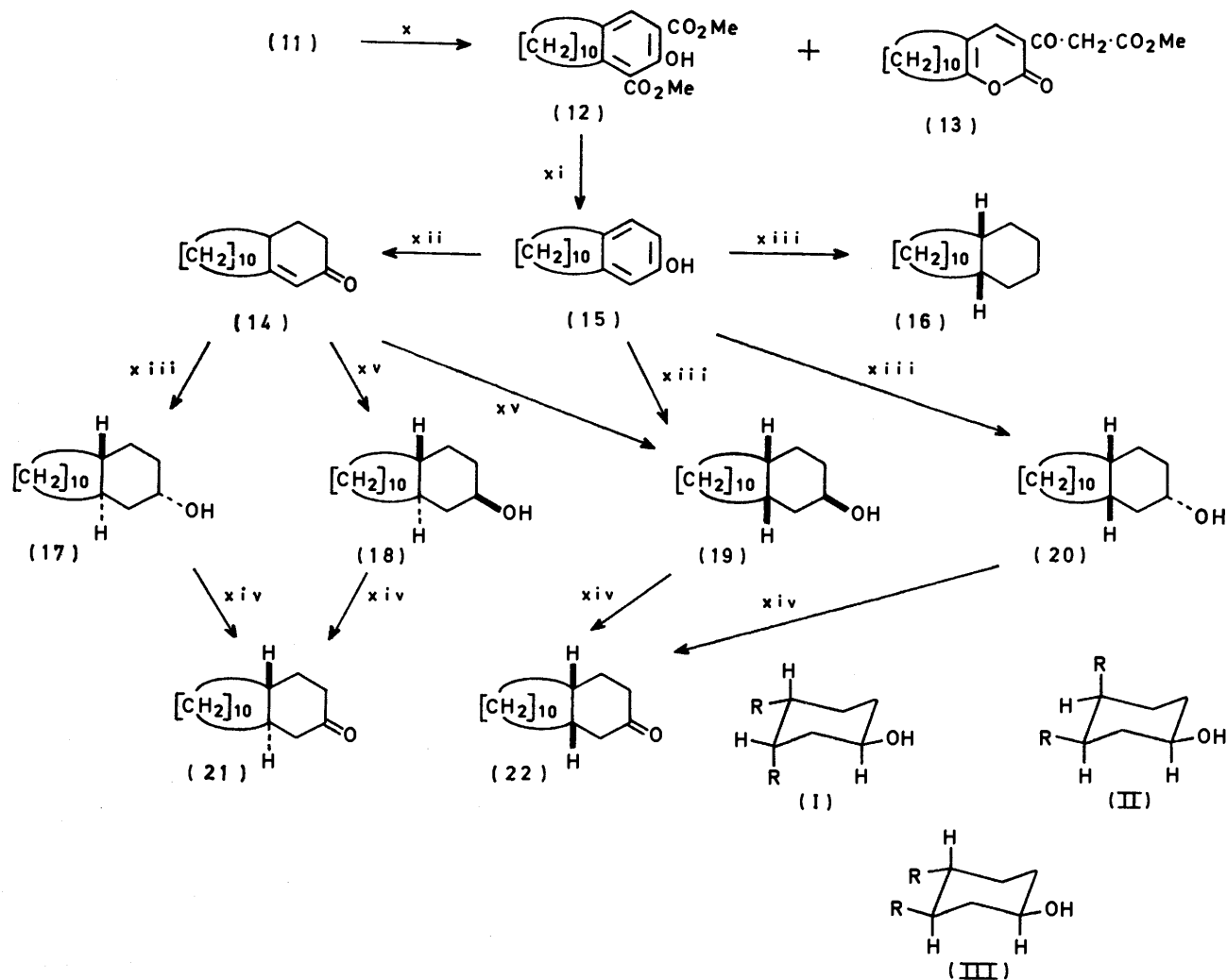
² C. Schwarzenbach, M. Zimmermann, and V. Prelog, *Helv. Chim. Acta*, 1951, **34**, 1954.

³ A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Synth.*, 1967, **47**, 20.

⁴ R. B. Turner, D. E. Nettleton, and R. Ferebee, *J. Amer. Chem. Soc.*, 1956, **78**, 5923.



SCHEME 1 Reagents: i, Me₂CO₂-NaH; ii, MeCO·CH:CH₂; iii, HCl; iv, (a) CH₂:CH-CN, (b) LiI; v, EtOH-H₂SO₄; vi, BrCH₂-CO₂-Et-Zn; vii, NC-CH₂-CO₂Et; viii, (a) Cl₂C:CH-CHO-H₂SO₄, (b) AcOH-HCl; ix, HCO₂Et-NaH



The compounds in this paper are all racemates: an arbitrary choice has been made of one enantiomer for illustration

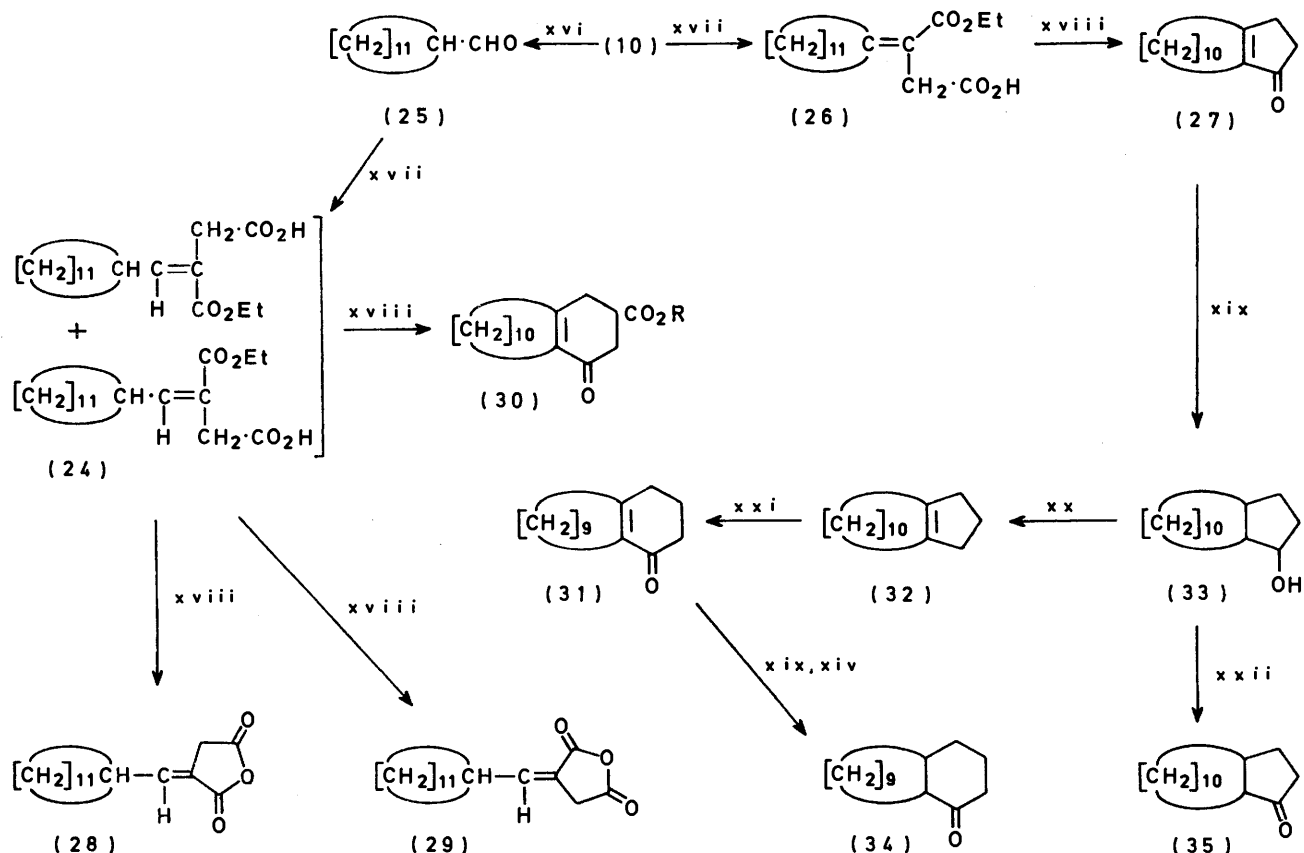
SCHEME 2 Reagents: x, OC(CH₂-CO₂Me)₂; xi, (a) NaOH, (b) heat with quinoline; xii, (a) Me₂SO₂-NaOH, (b) Li-NH₃(liq.)-Bu^oOH, (c) HCl; xiii, H₂-PtO₂; xiv, H₂CrO₄-Me₂CO; xv, Li-NH₃(liq.)-EtOH

compound (11) and methyl vinyl ketone leads to compound (14), behaviour quite different from that of the adduct (7) from the oxo-ester (6).

Hydrogenation⁸ of the phenol (15) under acidic conditions gave a mixture of the two alcohols (19) and (20) along with the hydrocarbon (16) formed by hydrogenolysis. The major product of the reduction was the *cis,cis*-* alcohol (20), which was obtained pure; this was expected since hydrogenation of benzene derivatives over platinum metals usually gives all-*cis*-cyclohexanes.¹¹ The n.m.r. spectrum of the mixture of alcohols (19) and

atoms in (19) and (20) compare favourably with those reported for the corresponding decalols.¹⁴ Considerable hydrocarbon (16) being obtained in the above reduction, the hydrocarbon (PtO₂) of the acetate of (15) gave only (16), and compound (15) was not affected by rhodium on alumina¹⁵ even under vigorous conditions.

Reduction of the ketone (14) with lithium-ammonia¹⁶ gave a 1 : 1 mixture of two alcohols (18) and (19) which was separated by preparative layer chromatography (p.l.c.). Oxidation of (19) yielded the *cis*-ketone (22),



SCHEME 3 Reagents: xvi, (a) $\text{ClCH}_2\cdot\text{OEt-Mg}$, (b) HCO_2H ; xvii $(\text{CH}_3\text{-CO}_2\text{Et})_2\text{-NaH}$; xviii, polyphosphoric acid; xix, $\text{H}_2\text{-Raney Ni}$; xx, TsOH ; xxi, (a) O_3 , (b), KOH-EtOH ; xxii, $\text{Na}_2\text{Cr}_2\text{O}_7\text{-HOAc}$

(20) contained CHOH signals at τ 6.20 ($W_{\frac{1}{2}}$ 20 Hz) (19) and 6.55 ($W_{\frac{1}{2}}$ 20 Hz) (20), with intensity ratio 15 : 85. The widths ($W_{\frac{1}{2}}$) of both these signals indicate¹² that the H atoms are axial in each alcohol; compound (19) exists mainly in conformation (I; $\text{RR} = [\text{CH}_2]_{10}$), 1,3-axial interaction between the α -hydrogen atom and the methylene groups causing deshielding of the α -hydrogen atom.¹³ The major product (20) of the hydrogenation exists mainly in conformation (II; $\text{RR} = [\text{CH}_2]_{10}$). The values of the chemical shifts of the α -hydrogen

and the other product of the reduction was the *trans,cis*-compound (18) [τ 6.55 (CHOH , $W_{\frac{1}{2}}$ 20 Hz); preferred conformation (III)], which was oxidized to the *trans*-ketone (21). Hydrogenation of the unsaturated ketone (13) afforded the *trans,trans*-alcohol (17) [τ 5.95 (CHOH $W_{\frac{1}{2}}$ 10 Hz)], which was oxidized to the *trans*-ketone (21). The *cis*- and *trans*-ketones (21) and (22) could not be separated by t.l.c. (see below). Catalytic hydrogenation of compound (14) gave¹⁰ an oily mixture of (21)

¹³ L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, pp. 79, 237.

¹⁴ H. Feltkamp, N. C. Franklin, W. Kraus, and W. Brugel, *Annalen*, 1965, **683**, 75.

¹⁵ A. I. Meyers, W. Beverung, and G. Garcia-Munoz, *J. Org. Chem.*, 1964, **29**, 3427.

¹⁶ G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, 1964, **86**, 1761.

* The terms '*cis*' and '*trans*' here refer to the relative configurations of substituents attached to the cyclohexane ring.

¹¹ J. Fried and J. A. Edwards, 'Organic Reaction in Steroid Chemistry,' vol. 1, Van Nostrand-Reinhold, 1972, p. 137.

¹² N. C. Franklin and H. Feltkamp, *Angew. Chem. Internat. Edn.*, 1965, **4**, 774.

and (22), from which a crystalline product was not obtained.

Bicyclo[10.3.0]pentadec-1(12)-en-13-one (27) was prepared^{10,17} from cyclo-octadecanone, the use of NaH in the Stobbe reaction to form (26) greatly simplifying the experimental procedure. Treatment of the aldehyde (25)¹⁸ with diethyl succinate-sodium hydride yielded a mixture (24) of isomeric half-esters. Cyclisation of this mixture gave the expected ketone (30; R = Et), and also the two anhydrides (28) and (29). Hydrolysis of (30; R = Et) gave the corresponding acid (30; R = H), which resisted all attempts at decarboxylation. By use of Eschenmoser's procedures, hydrogenation of the ketone (27) yielded the alcohol (33), which on dehydration afforded the olefin (32). This was ozonised to the corresponding dione, which cyclised under alkaline conditions forming the unsaturated ketone (31).¹⁹ Oxidation of the alcohol (33) gave the corresponding ketone (35). This compound has been prepared^{10,20} by hydrogenation of the enone (27). Nozaki²⁰ assigned a *trans*-configuration to the compound since it was homogeneous (t.l.c. and g.l.c.), as was apparently our sample. However, since we were unable to separate the isomeric ketones (21) and (22) the material (35) obtained in these reactions may well be a mixture. Hydrogenation of the unsaturated ketone (31) yielded a mixture of the saturated ketones (34) and the corresponding alcohols.

The results of hydroxylation of these bicyclic alcohols and ketones are reported in the following paper.

EXPERIMENTAL

General experimental conditions and details of standard isolation procedures have been reported.²¹ Silica gel of grade M60 was used for column chromatography and un-baked Kieselgel PF_{254/366} for p.l.c.²² G.l.c. was performed on a 15% silicone oil column at 130 or 160 °C with a nitrogen flow-rate of 60 ml min⁻¹ (Pye 104 instrument). Liquid ammonia was purified by distillation from sodium and 'oxidation' implies treatment with chromic acid-acetone.

I.r. spectra were obtained with a Unicam SP 1000 instrument for solutions in carbon tetrachloride unless otherwise stated, and u.v. spectra for solutions in ethanol with a Cary 14M spectrophotometer. N.m.r. spectra were measured with a Perkin-Elmer R-14 or R-32 instrument for solutions in carbon tetrachloride solution unless otherwise stated. Mass spectra were recorded with an A.E.I. MS9 or Varian MAT CH-7 spectrometer. Light petroleum refers to the fraction b.p. 60–80 °C.

Methyl 2-Oxo-1-(3-oxobutyl)cyclododecanecarboxylate (7).—Dimethyl carbonate (54.0 g) was added dropwise to a stirred suspension of NaH (34.2 g of 60% suspension in oil) in benzene (400 ml). The mixture was heated to 70 °C, MeOH (10 drops) added, and the ketone (10) (54.6 g) in benzene (100 ml) added to the boiling mixture during 90

¹⁷ K. Biemann, G. Buchi, and B. H. Walker, *J. Amer. Chem. Soc.*, 1957, **79**, 5558.

¹⁸ M. De Botton, *Compt. rend.*, 1968, **267**, 337.

¹⁹ A. Eschenmoser, S. Afr. Pat. 6415/1967 (*Chem. Abs.*, 1969, **70**, 88108v); G. Ohloff, J. Becker, and K. H. Schulte-Elte, *Helv. Chim. Acta*, 1967, **50**, 705.

²⁰ H. Nozaki, T. Mori, R. Noyori, and M. Kawanisi, *Canad. J. Chem.*, 1967, **45**, 1804.

min. Boiling was continued for 1 h more and the mixture stirred overnight. HOAc (60 ml) and ice-water (400 ml) were then added. The organic layer was washed with H₂O. Distillation afforded the oxo-ester (6) (66.4 g; b.p. 118–123° at 0.3 mmHg) (lit.,² 92° at 0.02 mmHg). The oxo-ester (12 g) was mixed with methyl vinyl ketone (5.5 g) and cooled to 0 °C. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) (10 drops) was added. After 24 h Et₂O and H₂O were added. The organic layer afforded *compound* (7), needles (from hexane), m.p. 93.5–94° (8.5 g) (Found: C, 69.7; H, 9.8. C₁₈H₃₀O₄ requires C, 69.7; H, 9.7%), ν_{\max} 1 745, 1 725, 1 715, and 1 168 cm⁻¹; τ 6.35 (3 H, s, OMe), 7.75–8.30 (8 H, complex), 7.95 (3 H, s, COMe), and 8.72br (16 H); *m/e* 310 (4%, M⁺), 278 (4%), 253 (13%), 221 [7%; m* 193 (253 → 221)], 43 (100%), and 41 (80%).

12-Methylbicyclo[9.3.1]pentadec-11-en-15-one (8).—The diketone (7) (8.5 g) was boiled (24 h) with a mixture of HOAc (150 ml) and conc. HCl (25 ml). Chromatography [silica (200 g); EtOAc-light petroleum (1 : 4)] afforded the *ketone* (8) (5.7 g), yellow prisms, m.p. 50–51° (aq. EtOH) (Found: C, 82.2; H, 11.1. C₁₆H₂₆O requires C, 82.1; H, 11.1%); ν_{\max} 1 665 and 1 630 cm⁻¹; λ_{\max} 246 nm (ϵ 9 350); τ 7.25–8.10 (5 H, m, CH·CO and CH₂·C=C), 8.17 (3 H, s, Me), and 8.79br (18 H); *m/e* 234 (M⁺, 86%), 219 (23%), 216 (4%), 121 [100%; m* 62.5 (234 → 121)], 67 (84%), and 41 (83%).

3-(2-Oxocyclododecyl)propionitrile (5).—The β -oxo-ester (6) (1.0 g) was mixed with acrylonitrile (0.42 g) and DBN (1 drop) added. After 30 min more acrylonitrile (0.21 g) was added. Two hours later the solid was chromatographed [silica (70 g); EtOAc-light petroleum (1 : 4)] affording *methyl 1-(2-cyanoethyl)-2-oxocyclododecanecarboxylate* (0.86 g; m.p. 87°) (Found: C, 69.9; H, 9.3; N, 4.9. C₁₇H₂₇O₃N requires C, 69.6; H, 9.2; N, 4.8%); ν_{\max} 2 256, 1 747, 1 713, and 1 185 cm⁻¹; τ 6.25 (3 H, s, OMe), 7.80–8.40 (8 H, complex, CH₂·CO, CH₂·CH₂·CO, and CH₂·CN), and 8.70br (16 H); *m/e* 293 (M⁺, 5%), 262 (7%), 253 (12%), 221 [13%; m* 193 (253 → 221)], 151 (25%), and 41 (100%).

The ester (6) (10 g) was mixed with acrylonitrile (4.2 g) and DBN (5 drops) added. After 48 h the crude product was dissolved in 2,4,6-collidine (60 ml) containing LiI₂H₂O (18.0 g) and the solution boiled (16 h; N₂ atmosphere). The cold mixture was treated with HCl (20%, 180 ml) and benzene. The benzene layer was washed with dil. HCl. Chromatography [silica (250 g); EtOAc-light petroleum (1 : 4)] afforded *compound* (5) (6.7 g), m.p. 62–64° (from hexane) (Found: C, 76.8; H, 10.7; N, 6.0. C₁₅H₂₅NO requires C, 76.6; H, 10.6; N, 6.0%); ν_{\max} 2 255, 1 712, and 1 127 cm⁻¹; τ 7.35 (1 H, m, CH·CO), 7.65–7.85 (4 H, complex, CH₂·CN and CH₂·CO), 7.95–8.60 (6 H, complex, CH₂·CH₂·CO and CH₂·CH₂·CN), and 8.72br (14 H); *m/e* 235 (M⁺, 24%), 195 (42%), 98 (55%), 69 (49%), 55 (100%), and 41 (97%). The nitrile (5) (4.0 g) was boiled (64 h) in EtOH (40 ml) containing conc. H₂SO₄ (7 ml). *Ethyl 3-(2-oxocyclododecyl)propionate* (4) (4.4 g) had b.p. 148–150° at 0.2 mmHg; m.p. 32–35° (Found: C, 72.4; H, 10.8. C₁₇H₃₀O₃ requires C, 72.4; H, 10.6%); ν_{\max} 1 740, 1 712,

²¹ A. M. Bell, J. W. Browne, W. A. Denny, Sir Ewart R. H. Jones, A. Kasal, and G. D. Meakins, *J.C.S. Perkin I*, 1972, 2579; M. J. Ashton, A. S. Bailey, and Sir Ewart R. H. Jones, *J.C.S. Perkin I*, 1974, 1658.

²² J. W. Blunt, I. M. Clark, J. M. Evans, Sir Ewart R. H. Jones, G. D. Meakins, and J. T. Pinhey, *J. Chem. Soc.*, (C), 1971, 1136.

and 1 175 cm^{-1} ; τ 5.96 (2 H, q, J 7 Hz, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$), 7.35—7.95 (5 H, complex, $\text{CH}_2\cdot\text{CO}$), 8.00—8.46 (6 H, complex, $\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$), and 8.71br (17 H); m/e 282 (M^+ , 32%), 237 (38%), 195 (17%), 158 (90%), 88 (48%), and 55 (100%). The oxo-ester (4) (1.82 g) in benzene (20 ml) containing ethyl bromoacetate (3.34 g) was treated with Zn powder (1.3 g) and the mixture boiled for 3 h. Ethyl bromoacetate (3.34 g) and Zn (1.3 g) were then added and the boiling continued. Next day the product was chromatographed on silica and the u.v.-active fractions gave a yellow oil (368 mg). P.l.c. of this gave needles (60 mg), m.p. 55—63°, of ethyl 5-(2-oxocyclododecyl)-3-oxopentanoate (1) (Found: C, 70.5; H, 9.9%; M , 324. $\text{C}_{19}\text{H}_{32}\text{O}_4$ requires C, 70.4; H, 9.9%; M , 324); ν_{max} 1 742, 1 720, 1 681, 1 632, 1 190, and 1 165 cm^{-1} ; τ (CDCl_3) 5.83 (2 H, q, J 7 Hz, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$), 6.62 (2 H, s, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$), 7.33—8.10 (7 H, complex, $\text{CH}_2\cdot\text{CO}$ and $\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$), 8.18—8.48 (4 H, complex, $\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}$), and 8.72br (17 H, $[\text{CH}_2]_{14}$ and $\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$).

Reaction of Cyclododecanone with Ethoxyacetylene.—Ethoxyacetylene (3.0 g) in Et_2O (10 ml) was added to BuLi (20 ml of 2M-solution in hexane) in N_2 atmosphere. The mixture was cooled to -20°C and the ketone (10) (5.5 g) in Et_2O (10 ml) added. After 1 h the cooling bath was removed and the mixture stirred for a further 2 h. Water (50 ml) was then added followed by HCl (50 ml; 0.1M). The usual isolation gave a product (5.7 g) which was chromatographed [silica (170 g); EtOAc—light petroleum] affording 2-(1-hydroxycyclododecyl)cyclododecanone (75 mg), m.p. 158—159° (Found: C, 79.3; H, 11.9. $\text{C}_{24}\text{H}_{44}\text{O}_2$ requires C, 79.1; H, 12.1%); ν_{max} (Nujol) 3 520 (OH) and 1 682 cm^{-1} (H-bonded CO); τ (CDCl_3) 6.72 (1 H, s, exchanged with D_2O , OH), 7.31—7.53 (3 H, complex, $\text{CH}_2\cdot\text{CO}$ and $\text{CH}\cdot\text{CO}$), and 8.0—8.68 (40 H, complex); m/e 364 (M^+ , 8%), 346 (10%), 182 (100%), 111 (46%), 98 (75%), and 55 (85%). Further elution gave starting material (10) (4.2 g), followed by the crude adduct (1.2 g); ν_{max} 3 610, 3 500br, and 2 250 cm^{-1} . The carbinol (0.8 g) in Et_2O (10 ml) was shaken for 5 min with a mixture of HCl (conc.; 5 ml) and H_2O (5 ml) and left for 20 min. The Et_2O layer was washed with aq. K_2CO_3 and yielded a neutral oil which was chromatographed (silica; EtOAc—petrol). Ethyl cyclododecylideneacetate formed a pale yellow oil (0.3 g) (Found: C, 75.9; H, 10.9. $\text{C}_{16}\text{H}_{28}\text{O}_2$ requires C, 76.2; H, 11.1%); ν_{max} 1 722, 1 643, and 1 150 cm^{-1} ; λ_{max} 223 nm (ϵ 14 100); τ 4.40 (1 H, s, $\text{HC}=\text{C}$), 5.95 (2 H, q, J 7 Hz, $\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$), 7.31 (2 H, t, J 7 Hz, $\text{CH}_2\cdot\text{C}=\text{C}$), 7.82 (2 H, t, J 7 Hz, $\text{CH}_2\cdot\text{C}=\text{C}$), 8.40—8.92 (21 H, complex, $[\text{CH}_2]_9 + \text{O}\cdot\text{CH}_2\cdot\text{CH}_3$); m/e 254 (M^+ , 4%), 207 (10%), 164 [17%; m^* 107 (252 \rightarrow 164)], 128 [35%; m^* 65 (252 \rightarrow 128)], 55 (70%) and 41 (100%).

Reaction of the Ketone (5) with Ethyl Cyanoacetate.—The ketone (5) (1.18 g) and ethyl cyanoacetate (1.13 g) were boiled [Dean-Stark apparatus] in benzene (2 ml) containing ammonium acetate (1.0 g) for 3 days, more ammonium acetate (1 g lots) being added at 12 h intervals. Chromatography [silica; EtOAc—petrol (1 : 4)] yielded ethyl 14-amino-15-cyanobicyclo[10.4.0]hexadeca-12,14-diene-13-carboxylate (2) (319 mg), yellow prisms (EtOAc—hexane), m.p. 130—133° (Found: C, 72.5; H, 9.5; N, 8.3. $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_2$ requires C, 72.7; H, 9.1; N, 8.5%); ν_{max} 2 320, 2 210, 1 665, 1 608, and 1 282 cm^{-1} ; λ_{max} 327 nm (ϵ 17 500); τ -0.75 (2 H, s, NH), 5.83 (2 H, q, J 7 Hz, $\text{CH}_3\cdot\text{CH}_2\cdot\text{O}$), 7.23 (2 H, m), 7.65—7.92 (6 H, complex), and 8.3—9.0 (19 H); m/e 330 (M^+ , 100%), 285 [12%; m^* 246 (330 \rightarrow 285)], 206 [67%; m^* 129 (330 \rightarrow 206)], 119 (98%), 117

(98%), and 41 (52%). Further elution gave a sticky solid (700 mg) containing ethyl cyanoacetate. Recrystallisation (Et_2O —hexane) gave a yellow solid (300 mg), m.p. 135—145°. P.l.c. [CH_2Cl_2 — Me_2CO — MeOH (80 : 8 : 2)] followed by recrystallisation (Et_2O —hexane) afforded 12-aminobicyclo[9.3.1]pentadec-11-en-15-one (3), plates, m.p. 138—143° (Found: C, 76.6; H, 10.5; N, 6.1. $\text{C}_{15}\text{H}_{25}\text{NO}$ requires C, 76.6; H, 10.6; N, 6.0%); ν_{max} 3 430, 3 235, 3 115, 1 695, and 1 672 cm^{-1} ; λ_{max} 254 nm (ϵ 5 760); τ (CDCl_3) 2.90br (2 H, s, NH, exchanged D_2O), 7.48—7.93 (7 H, complex), and 8.62br (16 H); m/e 235 (M^+ , 41%), 178 (10%), 164 (15%), 136 (50%), 124 (49%), and 111 [100%; m^* 52.5 (235 \rightarrow 111)].

Dimethyl 14-Hydroxybicyclo[10.4.0]hexadeca-1(16),12,14-triene-13,15-dicarboxylate (12) and Methyl 3-Oxo-3-{14-oxo-13-oxabicyclo[10.4.0]hexadeca-1(12),15-dien-15-yl}-propionate (13).—2-Hydroxymethylenecyclododecanone (11) was prepared* (77%) from cyclododecanone and ethyl formate by using $\text{NaH}\cdot\text{Et}_2\text{O}$ rather than NaOMe ; b.p. 101—102° at 0.6 mmHg (lit.,* 110° at 0.13 mmHg); the oil later solidified; m.p. 65—68°; τ (keto form) 0.51 (d, J 2 Hz, CHO), 7.40 (m, $\text{CH}\cdot\text{CHO}$); τ (enol form) 1.50 (s, $\text{C}=\text{CH}$), 7.73 (4 H, q, J 7 Hz), 8.23 (2 H, m), and 8.60br (14 H) (90% enol form). Compound (11) (10.5 g) and dimethyl 3-oxopentanedioate (8.7 g) were dissolved in Et_2O (50 ml) and added dropwise to a stirred suspension of NaH (2.2 g; 60% in oil; 0.055 mol) in Et_2O (100 ml). The mixture was stirred at 0°C for 2 h and then at room temp. for 5 days. EtOH (10 ml) was then added followed by aq. 2M-HCl. Isolation (Et_2O) afforded an oil which solidified on trituration with hexane. The solid (7.2 g) was collected and the residue chromatographed (silica; EtOAc—petrol) affording more solid (2.8 g). Compound (12) (10 g, 58%) formed needles (from hexane), m.p. 119—120.5° (Found: C, 69.3; H, 8.3. $\text{C}_{20}\text{H}_{28}\text{O}_5$ requires C, 69.0; H, 8.1%); ν_{max} 3 210, 1 742, 1 685, 1 622, 1 385, and 1 290 cm^{-1} ; λ_{max} 212, 248, and 318 nm (ϵ 30 200, 10 500, and 5 100); τ -0.55 (1 H, s, OH, exchanged with D_2O), 2.40 (1 H, s, ArH), 6.08 (3 H, s, MeO), 6.14 (3 H, s, MeO), 7.40 (4 H, complex, $\text{CH}_2\cdot\text{C}=\text{C}$), and 8.50br (16 H). Further elution of the column gave the pyrone (13) (0.5 g), needles (EtOAc—petrol), m.p. 81.5—83° (Found: C, 68.3; H, 7.7. $\text{C}_{19}\text{H}_{26}\text{O}_5$ requires C, 68.3; H, 7.8%); ν_{max} 1 745, 1 730, 1 645, and 1 612 cm^{-1} ; λ_{max} 230sh and 350 nm (ϵ 4 000 and 13 200); τ (enol) -2.40 (s, OH, exchanged with D_2O) and 3.48 (s, $\text{HC}=\text{C}$); τ (keto) 6.11 (s, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{Me}$), 2.01 and 2.12 (1 H, $\text{C}=\text{CH}$), 6.22 and 6.30 (3 H, MeO), 7.50 (4 H, complex, $\text{CH}_2\cdot\text{C}=\text{C}$), and 8.20—8.60 (16 H); m/e 334 (M^+ , 100%), 306 [17%; m^* 280.5 (334 \rightarrow 306)], 303 [14%; m^* 274 (334 \rightarrow 303)], 274 [50%; m^* 225 (334 \rightarrow 274)], 261 [46%; m^* 204.5 (334 \rightarrow 261)], and 41 (38%). Use of diethyl 3-oxopentanedioate afforded after chromatography the corresponding diethyl ester (41%), m.p. 117—118° (lit.,* 105°); m/e 376 (M^+ , 17%), 331 (45%), 330 (100%), 302 [27%; m^* 276.5 (330 \rightarrow 302)], 284 (53%), and 256 (31%). Further elution gave ethyl 3-oxo-3-{14-oxo-13-oxabicyclo[10.4.0]hexadeca-1(12),15-dien-15-yl}propionate (0.69 g), needles (EtOAc—petrol), m.p. 105—105.5° (Found: C, 69.1; H, 7.9. $\text{C}_{20}\text{H}_{28}\text{O}_5$ requires C, 69.0; H, 8.1%); ν_{max} 1 743, 1 730, 1 643, 1 613, and 1 222—1 195 cm^{-1} ; λ_{max} 228sh and 351 nm (ϵ 4 500 and 12 300); τ (enol) -2.49 (s, OH) and 3.52 (s, $\text{HC}=\text{C}$); τ (keto) 6.17 (s, $\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{R}$), 2.03 and 2.12 (1 H, $\text{HC}=\text{C}$), 5.80 (2 H, complex, $\text{CH}_3\cdot\text{CH}_2\cdot\text{O}$), 7.50 (4 H, complex, $\text{CH}_2\cdot\text{C}=\text{C}$), and 8.20—8.65 (19 H); m/e 348 (M^+ , 100%), 320 (17%), 303 (10%), and 274 (33%).

Bicyclo[10.4.0]hexadeca-1(16),12,14-trien-14-ol (15).—The diester (12) was hydrolysed (NaOH-EtOH-H₂O; 18 h) affording the corresponding dicarboxylic acid, m.p. 246–248° (lit.,⁸ 232°); *m/e* 320 (*M*⁺, 13%), 302 (67%), 284 [96%; *m*^{*} 267 (302 → 284)], and 258 (100%). The acid (9.3 g) was boiled in quinoline (50 ml) for 40 min; the solution was poured into H₂O (50 ml) and HCl (100 ml: conc. acid diluted with equal vol. H₂O) was added. Extraction with ether and chromatography [silica (200 g); EtOAc-petrol] yielded the phenol (15) (87%), m.p. 74–74.5° (lit.,⁸ 70°); λ_{\max} 200, 220, and 280 nm (ϵ 39 000, 7 100, and 2 000); *m/e* 232 (*M*⁺, 40%), 147 (19%), 121 (41%), and 57 (100%).

Bicyclo[10.4.0]hexadec-12-en-14-one (14).—The phenol (15) was methylated (Me₂CO-NaOH-Me₂SO₄) affording the methyl ether (90%), b.p. 136° at 0.2 mmHg (Found: C, 83.1; H, 10.6. C₁₇H₂₆O requires C, 82.9; H, 10.6%); ν_{\max} 1 615 and 1 290 cm⁻¹; λ_{\max} 200, 221, 279, and 286sh nm (ϵ 41 600, 7 900, 1 800, and 1 700); τ 3.05 [1 H, d, *J* 8 Hz, C(16)H], 3.42 [1 H, s, C(13)H], 3.45 [1 H, dd, *J* 8 and 2 Hz, C(15)H], 6.30 (3 H, s, MeO), 7.42 (4 H, complex, CH₂C=C), 8.32 (4 H, complex, CH₂·CH₂·C=C), and 8.57br (12 H); *m/e* 246 (*M*⁺, 100%). A solution of the ether (4.85 g) in dry Et₂O and dry Bu^tOH (1:1; 100 ml) was added to dry distilled liquid NH₃ (500 ml) containing Et₂O and Bu^tOH (1:1; 300 ml). The mixture was stirred (15 min) and then Li (3.0 g) added during 20 min. The mixture was stirred overnight and the NH₃ allowed to evaporate. EtOH (100 ml) and H₂O (300 ml) were added and the product isolated (Et₂O). The crude enol ether was boiled (3 h) in MeOH (125 ml) containing H₂O (1.5 ml) and HCl (conc.; 1 ml). The MeOH was evaporated off and the products were isolated (Et₂O) and separated [silica (200 g); EtOAc-petrol]. The first fractions contained hydrocarbons (0.88 g) and further elution gave the crude $\beta\gamma$ -unsaturated ketone as a sticky solid (0.25 g) that was not fully characterized (ν_{\max} 1 722 cm⁻¹; τ 7.29 (2 H, s, C=CH₂·CO), 7.67 (4 H, s), 7.85 (4 H, m), and 8.62br (16 H); *m/e* 234 (*M*⁺, 100%), 192 (11%), and 110 [45%; *m*^{*} 51.5 (234 → 110)]}. This was followed by the $\alpha\beta$ -unsaturated ketone (14) (2.35 g), needles (from hexane), m.p. 80–81° (lit.,^{9,10} 77°) (Found: C, 82.3; H, 11.2. Calc. for C₁₆H₂₆O: C, 82.1; H, 11.1%); ν_{\max} 1 680 and 1 628 cm⁻¹; λ_{\max} 239 (ϵ 15 100), τ 4.26 (1 H, s, HC=C), 7.55 (2 H, t, *J* 6 Hz, CH₂·CO), 7.76 (2 H, m, CH₂·CH₂·CO), 7.88–8.11 (3 H, m, CH₂C=C), and 8.58br (18 H); *m/e* 234 (*M*⁺, 67%), 192 (12%), 147 (36%), 117 (41%), 110 (66%), and 41 (100%). The semicarbazone formed needles, m.p. 206–207° (from MeOH) (Found: C, 70.0; H, 9.9; N, 14.4. C₁₇H₂₆N₃O requires C, 70.1; H, 10.0; N, 14.4%).

(1*RS*,12*SR*,14*SR*)-*Bicyclo[10.4.0]hexadecan-14-ol* (20).—A solution of the phenol (15) (1.5 g) in EtOH (30 ml) was boiled (30 min) with Raney Ni (1.5 g). The Ni was removed, the solution evaporated, and the purified material hydrogenated [1 atm; 18 h; PtO₂ (0.15 g)] in HOAc (30 ml). The solution was diluted with water and extracted (Et₂O), and the neutral fraction chromatographed [silica (60 g); EtOAc-petrol]. The hydrocarbon (16) [0.69 g; m.p. 38–41° (lit.,⁸ 42°)] was eluted first, followed by a solid (0.60 g) which was shown (n.m.r.) to be a mixture (85:15) of compounds (20) and (19). Two recrystallisations (EtOAc-hexane) afforded the pure alcohol (20), needles, m.p. 123–124° (lit.,⁸ 124°), ν_{\max} 3 620 and 3 500 cm⁻¹; τ 6.55 (1 H, *W*_{1/2} 20 Hz, CH·OH), 8.30–8.38 (4 H, complex), and 8.66br (25 H); *m/e* 220 (*M*⁺ - 18, 52%), 192 (4%), 178 (10%), and 94 (100%). Hydrogenation [EtOH-HOAc (100:5) as

solvent] afforded only 16% of the mixture of isomers (19) and (20). The alcohol (20) (206 mg) was oxidized (Na₂Cr₂O₇-HOAc) to the *cis*-ketone (22) (83%), m.p. 63.0–63.5° (lit.,⁸ 61°); ν_{\max} 1 720 cm⁻¹; τ 7.67–7.83 (4 H, complex, CH₂·CO), 7.95–8.34 (4 H, complex), and 8.63br (20 H); *m/e* 236 (*M*⁺, 56%), 218 (6%), 178 (17%), 96 (55%), 55 (77%), and 41 (100%). Acetylation (Ac₂O-pyridine) of the phenol (15) gave the *acetate*, b.p. 160–166° at 0.5 mmHg, m.p. 52–54° (from hexane) (Found: C, 78.8; H, 9.5%; *M*⁺, 274. C₁₈H₂₆O₂ requires C, 78.8; H, 9.5%; *M*, 274); ν_{\max} 1 770, 1 220, and 1 195 cm⁻¹. Hydrogenation of this acetate (HOAc; PtO₂; 1 atm) gave the hydrocarbon (16) (72%).

(1*RS*,12*SR*,14*RS*)-*Bicyclo[10.4.0]hexadecan-14-ol* (19) and (1*RS*,12*RS*,14*RS*)-*Bicyclo[10.4.0]hexadecan-14-ol* (18).—A solution of the unsaturated ketone (14) (3.6 g) in dry EtOH (48 ml) containing dry Et₂O (30 ml) was added to dry liquid NH₃ (150 ml). The mixture was stirred (10 min) and then Li (1.6 g) added during 30 min. After 1 h NH₄Cl (6 g) was added and the mixture poured into water. Extraction (Et₂O) and chromatography (silica; EtOAc-petrol) yielded a mixture (3.39 g) of alcohols. A sample (0.3 g) of this material was separated by p.l.c. [Et₂O-petrol (1:4) (multiple elution)]. The less polar band (138 mg) gave the *alcohol* (19), needles (EtOAc-hexane), m.p. 125–125.5° (Found: C, 80.3; H, 12.6. C₁₆H₃₀O requires C, 80.7; H, 12.6%); ν_{\max} 3 620 and 1 043 cm⁻¹; τ (CDCl₃) 6.15 (1 H, *W*_{1/2} 20 Hz, CH·OH), 8.10–8.18 (4 H, complex), and 8.65br (25 H); *m/e* 220 (100%, *M* - 18), 135 (40%), 94 (100%), 80 (94%), 55 (95%), and 41 (84%). The more polar band (128 mg) afforded the *alcohol* (18), needles (from EtOAc-hexane), m.p. 100–104° (Found: C, 80.9; H, 12.6. C₁₆H₃₀O requires C, 80.7; H, 12.6%); ν_{\max} 3 620, 1 108, 1 050, and 1 032 cm⁻¹; τ 6.55 (1 H, *W*_{1/2} 20 Hz, CH·OH), 8.03–8.25 (4 H, complex), 8.44 (1 H, s, OH), and 8.64br (24 H); *m/e* 220 (*M* - 18, 100%), 135 (16%), 94 (76%), 80 (49%), and 41 (34%). Jones oxidation of compound (19) afforded the *cis*-ketone (22), and oxidation of (18) gave the *trans*-isomer (21) (see later).

(1*RS*,12*RS*,14*SR*)-*Bicyclo[10.4.0]hexadecan-14-ol* (17).—The $\alpha\beta$ -unsaturated ketone (14) (1.0 g) was hydrogenated [1 atm; room temp.; PtO₂ (0.1 g), HOAc (100 ml)]. The product was separated [p.l.c.; EtOAc-petrol (1:4)]. The band of *R_F* 0.23 afforded the *alcohol* (17) (192 mg), needles (from EtOAc-hexane), m.p. 116–116.5° (Found: C, 80.8; H, 12.6. C₁₆H₃₀O requires C, 80.7; H, 12.6%); ν_{\max} 3 620, 1 088, and 1 060 cm⁻¹; τ (CDCl₃) 5.95 (1 H, *W*_{1/2} 10 Hz, CH·OH), 8.08–8.32 (3 H, complex), 8.40–8.53 (5 H, complex), and 8.65br (21 H); *m/e* 220 (*M*⁺ - 18, 94%), 135 (21%), 94 (100%), 80 (51%), and 55 (47%). The band of *R_F* 0.17 gave a solid (432 mg); the n.m.r. spectrum contained two signals in the CH·OH region at τ (CDCl₃) 6.15 and 6.5 (ratio 1:9) corresponding to a mixture of compounds (18) and (19). Oxidation of the alcohol (17) (43 mg) gave the *trans*-ketone (21), plates (from hexane), m.p. 43–45° (Found: C, 81.3; H, 11.8. C₁₆H₂₈O requires C, 81.4; H, 11.9%); ν_{\max} 1 720 cm⁻¹; τ 7.67–7.82 (4 H, complex, CH₂·CO), 7.94–8.33 (4 H, complex), and 8.62 (20 H); *m/e* 236 (*M*⁺, 100%), 178 (19%), 109 (41%), 96 (83%), 83 (74%), and 55 (83%).

Bicyclo[10.3.0]pentadec-1(12)-en-13-one (27).—Diethyl succinate (106 g) was added to NaH (24 g of 60% suspension in oil) in benzene (100 ml). Cyclododecanone (36.4 g) in benzene (100 ml) was added followed by EtOH (5 drops). Next day the usual work-up gave the half-ester (26) (47.5 g).

This was cyclised (polyphosphoric acid), affording the ketone (27), b.p. 129—130° at 0.3 mmHg (lit.,¹⁷ 161.5—163° at 3.5 mmHg); ν_{\max} 1 695 and 1 633 cm^{-1} ; m/e 220 (M^+ , 87%), 177 [75%]; m^* 142.5 (220 \rightarrow 177), 163 [100%]; m^* 121 (220 \rightarrow 163), 149 (85%), and 135 (80%).

16-Oxobicyclo[10.4.0]hexadec-1(12)-ene-14-carboxylic Acid (30; R = H).—Cyclododecanecarbaldehyde (25) had b.p. 80—86° at 0.2 mmHg (lit.,¹⁸ 153—155° at 20 mmHg) and was stored in the cold under N_2 . The aldehyde (3.0 g) in benzene (10 ml) was added to a suspension of NaH (2.0 g of 60% suspension in oil) in benzene (10 ml) containing diethyl succinate (9 ml) and the mixture heated to 60 °C for 3 h. The usual work-up gave the crude half-esters (2.58 g). The mixture of esters (6.8 g) was stirred (95 °C; 3 h) with polyphosphoric acid (50 ml). Chromatography [silica (200 g); EtOAc-petrol] gave, in order of elution, the anhydride (28), prisms (0.37 g) (from EtOAc-hexane), m.p. 101—102° (Found: C, 73.6; H, 9.3. $\text{C}_{17}\text{H}_{26}\text{O}_3$ requires C, 73.4; H, 9.4%). ν_{\max} 1 861, 1 846, 1 788, and 1 678 cm^{-1} ; λ_{\max} 227 nm (ϵ 12 600); τ 3.25 (1 H, dt, J 10 and 2 Hz, HC=C), 6.57 (2 H, d, J 2 Hz), 7.58 (1 H, m, HC=C), and 8.24—8.60 (22 H); m/e 278 (M^+ , 9%), 260 (3%), 250 (4%), 233 (4%), 55 (57%), and 41 (100%). Further elution afforded the isomeric anhydride (29), needles (0.44 g), m.p. 128—130° (from Ac_2O) (Found: C, 73.3; H, 9.4. $\text{C}_{17}\text{H}_{26}\text{O}_3$ requires C, 73.4; H, 9.4%). ν_{\max} 1 855, 1 846, 1 780, and 1 672 cm^{-1} ; λ_{\max} 220 nm (ϵ 7 400); τ 3.85 (1 H, dt, J 11 and 2 Hz, HC=C), 6.30 (1 H, m, HC=C), 6.55 (2 H, d, J 2 Hz, CH_2CO), and 8.65br (22 H); m/e 274 (M^+ , 4%), 250 (2%), 212 (20%), 194 (35%), 55 (98%), and 41 (100%). The ketone (30; R = Et) eluted next formed a yellow oil (1.7 g), ν_{\max} 1 740, 1 712, 1 673, 1 640, and 1 618 cm^{-1} ; λ_{\max} 242 nm (ϵ 9 200); τ 5.88 (2 H, q, J 7 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 7.15 (1 H, m, CHCO_2Et), 7.46—7.57 (4 H, complex, CH_2CO and $\text{CH}_2\text{C}=\text{C}$), 7.73 (4 H, t, J 7 Hz, $\text{CH}_2\text{C}=\text{C}$), and 8.19br (19 H); m/e 306 (M^+ , 24%), 233 (25%), 107 (44%), 74 (64%), 59 (98%), and 57 (100%). The semicarbazone formed needles, m.p. 174—176° (from MeOH) (Found: C, 66.2; H, 8.9; N, 11.3. $\text{C}_{20}\text{H}_{33}\text{N}_3\text{O}_3$ requires C, 66.1; H, 9.1; N, 11.6%). The ester was hydrolysed by boiling (24 h) with $\text{LiI}_2\text{H}_2\text{O}$ in collidine. The acid (30; R = H)

formed needles, m.p. 115—117° (Et₂O-hexane) (Found: C, 73.2; H, 9.2. $\text{C}_{17}\text{H}_{26}\text{O}_3$ requires C, 73.4; H, 9.3%); ν_{\max} 3 500—2 500, 1 713, 1 675, and 1 619 cm^{-1} ; λ_{\max} 246 nm (ϵ 11 000); τ 4.50br (1 H, OH, exchanged with D_2O), 7.00 (1 H, m, CHCO_2H), 7.34—7.42 (4 H, m, CH_2CO and $\text{CH}_2\text{C}=\text{C}$), 7.67 (4 H, t, J 6 Hz, $\text{CH}_2\text{C}=\text{C}$), and 8.58br (16 H); m/e 278 (M^+ , 76%), 233 (28%), 222 [22%]; m^* 177 (278 \rightarrow 222), 221 (21%), and 107 (100%).

Bicyclo[9.4.0]pentadec-1(11)-en-12-one (31).—The ketone (27) was hydrogenated to form (33), m.p. 104—105° (lit.,¹⁹ 104—105°). Dehydration afforded the olefin (32), b.p. 97—98° at 0.15 mmHg, and ozonolysis of (32) gave a 60% yield of the corresponding diketone, m.p. 65—67° (lit.,¹⁹ 60—62°). This diketone was cyclised (EtOH-KOH) affording the unsaturated ketone (31), b.p. 118—122° at 0.05 mmHg (lit.,¹⁹ 112—115° at 0.02 mmHg); ν_{\max} 1 670, 1 614, and 1 368 cm^{-1} ; λ_{\max} 249 nm (ϵ 11 800); m/e 220 (M^+ , 46%), 177 [38%]; m^* 142.5 (220 \rightarrow 177), 163 [100%]; m^* 121 (220 \rightarrow 163), 149 (33%), and 41 (61%).

Bicyclo[10.3.0]pentadecan-13-one (35).—Oxidation ($\text{K}_2\text{Cr}_2\text{O}_7\text{-HOAc}$) of the alcohol (33) afforded (35), b.p. 144—146° at 1.0 mmHg (lit.,²⁰ 120—125° at 0.15 mmHg); ν_{\max} 1 745 and 1 410 cm^{-1} ; τ 7.89—8.25 (6 H, complex, CH_2CO and $\text{CH}_2\text{CH}_2\text{CO}$) and 8.64br (20 H); m/e 222 (M^+ , 18%), 96 [12%]; m^* 41.5 (222 \rightarrow 96), 83 (100%), and 55 (16%). The semicarbazone formed prisms ($\text{CHCl}_3\text{-MeOH}$), m.p. 218—220° (lit.,²⁰ 197—198°) (Found: C, 68.5; H, 10.4; N, 14.7. Calc. for $\text{C}_{16}\text{H}_{29}\text{N}_3\text{O}$: C, 68.8; H, 10.4; N, 15.1%).

Bicyclo[9.4.0]pentadecan-12-one (34).—Hydrogenation of the unsaturated ketone (31) (2.0 g) in MeOH (20 ml) containing m-NaOH (0.2 ml) and Raney Ni (1 atm; 40 h) gave a mixture of saturated ketone and alcohols. The mixture was oxidized and the resulting ketone boiled (18 h) with MeOH (30 ml), H_2O (5 ml), and KOH (5 g). The ketone (34) had b.p. 144—148° at 0.5 mmHg (Found: C, 81.3; H, 11.7. $\text{C}_{15}\text{H}_{26}\text{O}$ requires 81.1; H, 11.7%); ν_{\max} 1 716 cm^{-1} ; τ 7.55—7.97 (3 H, complex, CHCO), 8.02—8.28 (3 H, complex, CHCO), and 8.57br (20 H); m/e 222 (M^+ , 18%), 123 (5%), 110 (11%), and 97 (100%).

[6/1270 Received, 1st July, 1976]