A Synthetic Route to 3,7-Disubstituted Bicyclo[3.3.2]decanes

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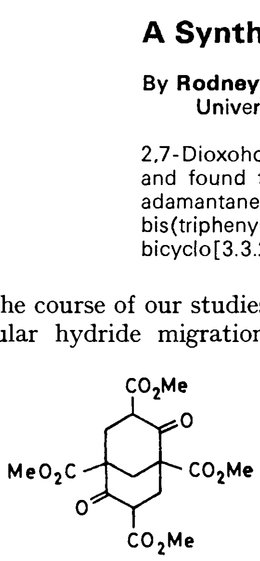
2,7-Dioxohomoadamantan-1,3,6,8-tetracarboxylic acid has been prepared in good yield from Meerwein's ester, and found to undergo specific 3,6-bisdecarboxylation. Wolff–Kishner reduction of the product gives homoadamantane-1,8-dicarboxylic acid. Treatment of the corresponding bis-acid chloride with chlorocarbonylbis(triphenylphosphine)rhodium gives 1,8-dichlorohomoadamantane, which is readily converted into 7-methylenebicyclo[3.3.2]decan-3-one in a base-induced fragmentation reaction.

IN the course of our studies on the mechanism of transannular hydride migrations in bridged-ring systems[1] we had need of certain bicyclo[3.3.2]decanes functionalised at both the 3- and the 7-position. Synthetic routes[2] to this ring system are sparse, particularly those derivatives with specific functionality on both trimethylene bridges, so we have devised a new synthesis using the readily-available Meerwein ester[3] (1) (tetramethyl 2,6-dioxobicyclo[3.3.1]nonane-1,3,5,7-tetracarboxylate) as starting material.



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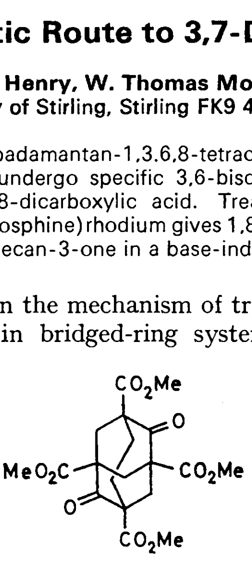

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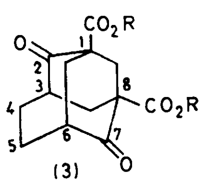

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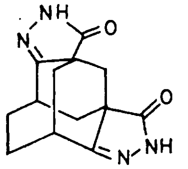

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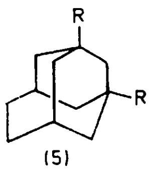

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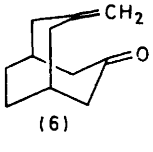

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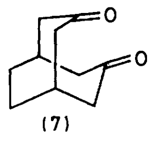

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Treatment of the ester (1) with sodium hydride and 1,2-dibromoethane[4] produced the dioxohomoadamantanetetracarboxylate (2) in good yield. Subsequent hydrolysis with aqueous acid gave the corresponding tetracarboxylic acid, which at 270—280° underwent

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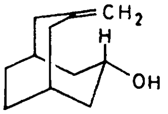
[1] See M. P. Doyle and W. Parker, *Chem. Comm.*, 1970, **755**, and references therein.

[2] (*a*) K. Alder, S. Hartung, and G. Hausmann, *Chem. Ber.*, 1956, **89**, 1972; however see M. P. Doyle and W. Parker, *Tetrahedron Letters*, 1970, 945; (*b*) L. Wegmann, *Dechemia Monograph*, 1959, **35**, 84; (*c*) G. Schroeder, *Angew. Chem. Internat. Edn.*, 1963, **2**, 481; G. Schroeder, R. Merenyi, and J. F. M. Oth, *Tetrahedron Letters*, 1964, 773; J. F. M. Oth, R. Merenyi, H. Roettele, and G. Schroder, *ibid.*, 1968, 3941; (*d*) R. Aumann, *Angew. Chem. Internat. Edn.*, 1971, **10**, 188; (*e*) M. J. Goldstein, S. Tomoda, and G. Whittaker, *J. Amer. Chem. Soc.*, 1974, **96**, 3676; (*f*) K. H. Baggaley, W. H. Evans, S. H. Graham, D. A. Jones, and D. H. Jones, *Tetrahedron*, 1968, **24**, 3445; however see R. G. Bingham and P. von R. Schleyer, *J. Org. Chem.*, 1971, **36**, 1198; R. Bishop, *J.C.S. Perkin I*, 1974, 2364; (*g*) B.P. 1,104,058; (*h*) M. P. Doyle and W. Parker, *Chem. Comm.*, 1969, 319; (*i*) G. A. Russell and R. G. Keske, *J. Amer. Chem. Soc.*, 1970, **92**, 4460; (*j*) N. J. Leonard and J. C. Coll, *J. Amer. Chem. Soc.*, 1970, **92**, 6685; J. C. Coll, Del. R. Crist, M. de C. G. Barrio, and N. J. Leonard, *ibid.*, 1972, **94**, 7092; (*k*) H. Schmid, J. Szindely, and A. Pryde, Special Lectures, XXIIIrd International Congress of Pure and Applied Chemistry, Boston 26—30th July, 1971, Butterworths.

[3] H. Meerwein, F. Kiel, G. Klosgen, and E. Schoch, *J. prakt. Chem.*, 1922, **104**, 161.

[4] (*a*) L. G. Humber, G. Myers, L. Hawkins, C. Schmidt, and M. Boulerice, *Canad. J. Chem.*, 1964, **42**, 2852; (*b*) B. Vogt, *Tetrahedron Letters*, 1968, 1579.

smooth regiospecific decarboxylation[5] to 2,6-dioxohomoadamantane-1,8-dicarboxylic acid (3; R = H). The corresponding bispyrazolone (4) was then treated with strong alkali[6] to give, after acidification, a dicarboxylic acid whose identification as (5; R = CO_2H) is fully supported by *X*-ray crystallographic analysis of the corresponding dimethyl ester.* Attempts to convert this system (5; R = CO_2H) into (5; R = halogen) by modified Hunsdiecker[8] and Kochi reactions[9] gave poor yields and mixtures of products; however, when the bis-acid chloride (5; R = COCl) was treated with a catalytic amount of chlorocarbonylbis(triphenylphosphine)rhodium[10] at 250°, a smooth reaction ensued, producing the desired bis-bridgehead chloride (5; R = Cl) in 67% yield. The ^{13}C n.m.r. spectrum[11,]† of the 1,8-dichlorohomoadamantane thus obtained showed the five-signal pattern expected. Subsequent treatment of (5; R = Cl) with aqueous sodium hydroxide[12] gave 7-methylenebicyclo[3.3.2]decan-3-one (6), which, either by oxidation with ruthenium tetraoxide or by ozonolysis, is readily converted into the corresponding 3,7-dione (7). The expected transannular behaviour of these compounds is illustrated by the ready preparation of the *exo*-alcohol (8) and its cyclisation[13] to homoadamantan-1-ol (9), identical with an authentic sample.[14]



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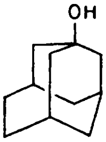

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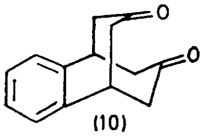
Föhlisch[15] and his co-workers have recently published a short synthesis of 5,6,8,9-tetrahydro-5,9-propanobenzocycloheptene-7,11-dione (10) which involved successive treatment of phthalaldehyde with dimethyl acetonedicarboxylate. The product from this double Aldol–double Michael reaction on hydrolysis and decarboxylation yielded (10). However, in our hands this is not yet a practicable route to the simple nonbenzenoid system.



(10)

EXPERIMENTAL

I.r. spectra were recorded on Perkin-Elmer 157G and 457G spectrophotometers. N.m.r. were determined for solution in carbon tetrachloride or deuteriochloroform with a Perkin-Elmer R10 or R24 spectrometer (tetramethylsilane as internal standard). Mass spectra were determined by the P.C.M.U., Harwell.

Analytical g.l.c. was performed with a Perkin-Elmer F11 instrument [2 m stainless steel column of 5% FFAP on Chromosorb W (80—100 mesh); carrier gas, nitrogen; inlet pressure 20 lb in^{-2}].

Tetramethyl 2,7-*Dioxotricyclo*[4.3.1.1^{3,8}]*undecane*-1,3,6,8-*tetracarboxylate* (2).—Sodium hydride (32 g of a 60% dispersion in oil) was washed free of oil with light petroleum and then stirred, under nitrogen, while a solution of Meerwein's ester[3] (1) (100 g) in anhydrous dioxan (750 ml) was added dropwise. When hydrogen evolution had ceased, freshly-distilled 1,2-dibromoethane (750 ml) was added in portions; the mixture was then heated at 110° for 24 h and filtered warm. Removal of the solvent *in vacuo* and trituration of the resultant gum with methanol gave a crystalline product which was recrystallised from methylene chloride to give the *dione tetraester* (2) as white needles (67 g), m.p. 255—256° (Found: C, 55·35; H, 5·5. $C_{19}H_{22}O_{10}$ requires C, 55·6; H, 5·4%); M^+ 410; $\nu_{max.}$ 1740, 1715, 1260, 1070, 1030, 957, and 930 cm^{-1}.

Dimethyl 2,7-*Dioxotricyclo*[4.3.1.1^{3,8}]*undecan*-1,8-*dicarboxylate* (3; R = Me).—A solution of the tetraester (2) (66·2 g) in acetic acid (300 ml), concentrated hydrochloric acid (100 ml), and water (100 ml) was heated under reflux for 16 h then evaporated to dryness *in vacuo*; the residue was then heated at 270—280° for 45 min, after which CO_2 evolution had ceased. The resultant crude dicarboxylic acid (3; R = H) was then converted by standard treatment with methanol–concentrated sulphuric acid into the *diester* (3; R = Me) (43 g), which crystallised from ethanol in needles, m.p. 254—255° (Found: C, 60·95; H, 5·95. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·15%); $\nu_{max.}$ (Nujol) 1742, 1717, 1288, 1140, 1100, 1020, and 970 cm^{-1}.

The corresponding *bispyrazolone* (4), prepared in quantitative yield by treatment of (3; R = CH_3) with hydrazine hydrate in the usual manner, crystallised from ethanol in needles, m.p. 336—227° (decomp.) (Found: C, 60·2; H, 5·5. $C_{13}H_{14}N_4O_2$ requires C, 60·45; H, 5·45%); $\nu_{max.}$ (Nujol) 3510, 3230, 1700, 1679, 1620, 1325, 1280, 1205, 1155, 1105, 905, and 740 cm^{-1}.

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* Apart from confirming the structure of (5; R = CO_2Me) the most significant finding from the *X*-ray crystallographic analysis (*R* factor 0·069) is that, in the solid state, the homoadamantane skeleton has virtual C_{2v} symmetry, *e.g.* the ethylene bridge shows a torsion angle of $-2°$ (*cf.* ref. 7) (R. S. Henry, J. Murray-Rust, and P. Murray-Rust, *Acta Cryst.*, in the press).

† We are indebted to the S.R.C.-supported ^{13}C n.m.r. service operated by the Chemistry Department, University of Edinburgh, for these spectra.

[5] (*a*) J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, 1966, **88**, 3522; (*b*) J. R. Wiseman and W. A. Peltcher, *ibid.*, 1970, **92**, 956; (*c*) O. Bottger, *Ber.*, 1937, **70B**, 314; (*d*) ref. 4*b*.

[6] See ref. 3 and S. Landa, *Sci. Papers Inst. Chem. Tech. Prague*, 1964, 31; S. Landa and J. Kiefmann, *Coll. Czech. Chem. Comm.*, 1970, **35**, 1005.

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[11] G. E. Hawkes, R. A. Smith, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1276.

[12] A. R. Gagneux and R. Meier, *Tetrahedron Letters*, 1969, 1365; H. Hamill, A. Karim, and M. A. McKervey, *Tetrahedron*, 1971, **27**, 4317.

[13] M. Eakin, J. Martin, and W. Parker, *Chem. Comm.*, 1965, 206.

[14] J. Janjatovič, D. Skare, and Z. Majerski, *J. Org. Chem.*, 1974, **39**, 651, and references therein; we thank Professor Majerski for a comparison sample.

[15] B. Föhlisch, U. Dukek, I. Graessle, B. Novotny, E. Schupp, G. Schwaiger, and E. Widmann, *Annalen*, 1973, 1839.

Tricyclo[4.3.1.1^{3,8}]*undecane*-1,8-*dicarboxylic Acid* (5; R = CO_2H).—The bispyrazolone (4) (35 g) was thoroughly mixed with powdered sodium hydroxide (35 g), water (22 ml) was added, and the mixture was heated in an autoclave (1500 ml) at 210° for 15 h. The cooled product was dissolved in water and acidified to pH 1 with aqueous hydrochloric acid, and the crude acid was filtered off, dried, and recrystallised from dioxan to give the *dicarboxylic acid* (5; R = CO_2H) as needles (23 g), m.p. 316—317°; $\nu_{max.}$ (Nujol) 3600—2400, 1715, 1390, 1290, 1260, and 1220 cm^{-1}.

The *dimethyl ester* (5; R = CO_2Me), prepared with diazomethane, gave white needles, m.p. 188—189° (Found: C, 67·5; H, 8·15. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%); δ_C ($CDCl_3$) 31·06, 32·98, 38·63, 38·95, 41·61, 51·74, and 178·17 p.p.m.

1,8-*Dichlorotricyclo*[4.3.1.1^{3,8}]*undecane* (5; R = Cl).—Oxalyl chloride (3 ml) was added to a stirred suspension of the dicarboxylic acid (5; R = CO_2H) (400 mg) in anhydrous benzene. The mixture was heated overnight under reflux, then the solvent and the excess of oxalyl chloride were removed *in vacuo*. The residual oil was then treated with chlorocarbonylbis(triphenylphosphine)-rhodium (70 mg) and slowly heated to 250°; gas evolution (presumably CO and HCl) was observed and a white solid sublimed into the neck of the flask. After 1 h at 250° the flask was cooled and the mixture and sublimate were dissolved in warm carbon tetrachloride and filtered through a short column of silica gel. Removal of the solvent left a white crystalline solid which was recrystallised from carbon tetrachloride to give the *bis-bridgehead dichloride* (5; R = Cl) (260 mg) as needles, m.p. (sealed tube) 159—160°; $\nu_{max.}$ (CS_2) 1355, 1315, 1299, 1248, 1207, 1170, 1070, 1061, 986, 957, 937, 931, 812, 800, and 720 cm^{-1}; δ_C ($CDCl_3$) 31·65, 32·56, 46·61, 56·00, and 69·06 p.p.m. The mass spectrum of the dichloride did not show a parent ion but the base peak corresponded to the loss of Cl^- (Found: *m/e*, 183·0939. $C_{11}H_{16}Cl$ requires 183·0941).

7-*Methylenebicyclo*[3.3.2]*decan*-3-*one* (6).—A solution of the dichloride (5; R = Cl) (500 mg) in dioxan (10 ml) was heated at 170—180° for 12 h with aqueous (10%) sodium hydroxide (10 ml) in a stainless steel autoclave (50 ml). The cooled mixture was diluted with water and thoroughly extracted with pentane, and the combined organic extracts were dried and evaporated. The residue was sublimed (10 Torr) to give the *methylene ketone* (6) (200 mg), m.p. (sealed tube) 159—160°; M^+ 164 (Found: C, 80·0; H, 9·65. $C_{11}H_{16}O$ requires C, 80·35; H, 9·8%); $\nu_{max.}$ (CCl_4) 3080, 1690, 1640, and 907 cm^{-1}; δ_H (CCl_4) 2·1 (4H, apparent t, *J* 2·5 Hz), 2·31br (3H, s), 2·40 (3H, apparent t, *J* 4 Hz), 2·50br (s) and 2·57 (apparent t) (*J* 5 Hz, *J'* 6·5 Hz), and 4·87 (2H, t, *J* 2 Hz); δ_C ($CDCl_3$) 213·7, 144·5, 118·6, 49·56, 42·15, 30·67, and 29·43 p.p.m.

Homoadamantan-1-*ol* (9).—A mixture of the methylene ketone (6) (100 mg), aluminium isopropoxide (1 g), and toluene (10 ml) was heated to reflux and the toluene was slowly distilled off through a Vigreaux column. After 3 h, 2 ml of toluene had been removed and the mixture was then cooled and stirred for 1 h with aqueous 10% sodium hydroxide before separating the layers. The aqueous layer was further extracted with ether (2 × 5 ml), and the combined extracts were dried (Na_2SO_4) and evaporated to *ca.* 3 ml. The solution was applied to a short column of silica gel and eluted first with pentane to remove residual toluene then with ether to provide a clear viscous oil (80 mg). This material had spectroscopic properties consistent with those of the expected methylene-*exo*-alcohol (8): $\nu_{max.}$ 3610 and 3470 cm^{-1} (OH str.); δ_H (CCl_4) 4·6br (s, $=CH_2$) and 4·5 (multiplet partially obscured $>C\mathit{H}\cdot OH$). However the integral of the n.m.r. spectrum suggested that this material also contained a non-olefinic component, possibly the cyclisation product (9). The crude material was therefore treated with toluene-*p*-sulphonyl chloride in pyridine, and the resultant crude toluenesulphonate was dissolved in M-sodium acetate in glacial acetic acid (10 ml) and kept for 24 h in a water-bath maintained at 40°. The mixture was then poured into water (50 ml) and extracted with ether. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, concentrated, and then added to a suspension of lithium aluminium hydride (200 mg) in ether (5 ml) and stirred for 1 h. The reaction was then quenched by cautious addition of saturated aqueous sodium sulphate. The ethereal solution was decanted, dried, and evaporated to give a white crystalline solid (40 mg), which was homogenous (g.l.c. and t.l.c.). This was identified as homoadamantan-1-ol (9) by g.l.c. and i.r. comparison with an authentic sample.[14]

Bicyclo[3.3.2]*decan*-3,7-*dione* (7).—The methylene ketone (6) was ozonised by the method of Pappas *et al.*[16] Ozone was passed into a cooled (−80°) solution of (6) (100 mg) in methylene chloride (5 ml) and methanol (5 ml) until the blue colour persisted. The mixture was then flushed with nitrogen until the blue colour vanished, before the addition (at −80°) of dimethyl sulphide (1 ml). The mixture was set aside overnight at room temperature, after which it gave a negative test for peroxides. It was evaporated under reduced pressure to leave a viscous oil, which was applied to a short column of silica gel. Elution with chloroform then gave the *dione* (7) (42 mg), which crystallised from ether in needles, m.p. (sealed tube) 248—250°; $\nu_{max.}$ (CCl_4) 1704, 1420, 1410, 1344, 1290, 1215, and 1165 cm^{-1}; δ_H ($CDCl_3$) 2·25br (*ca.* 4H, s) and 3·58br (*ca.* 8H, s) (Found: M^+, 166·0999. $C_{10}H_{14}O_2$ requires *M*, 169·0994).

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[16] J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Letters*, 1966, 4273.