An Alternative Synthesis of 2-Oxabicyclo[3.2.1]oct-3-enes

By **Paul Barraclough** and **Douglas W. Young,*** School of Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ

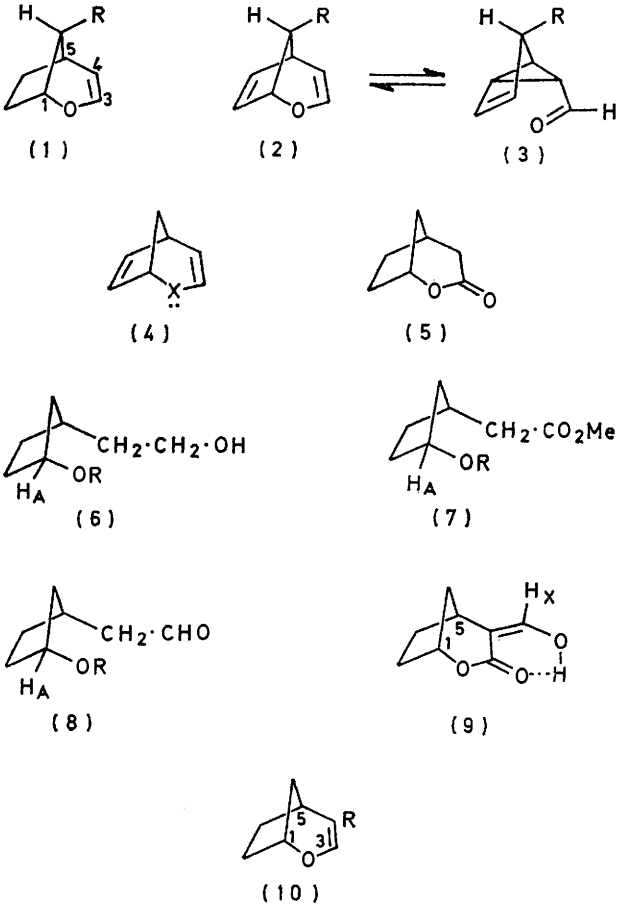
The acyl-lactone rearrangement has been employed in a synthesis of 2-oxabicyclo[3.2.1]oct-3-enes.

KLUMPP *et al.*[1] have synthesised 8-t-butoxy-2-oxabicyclo[3.2.1]oct-3-ene (1; R = Bu^{t}O) by reduction of the equilibrium mixture (2; R = Bu^{t}O) ⇌ (3; R = Bu^{t}O) with di-imide. Other substituted compounds of this type have been prepared by photolytic means.[2] Since we were interested [3] in compounds of the general structure (4) as possible bishomoaromatic species, the unsubstituted compound (1; R = H) was required as a reference compound.

When we investigated direct synthesis by applying the method of Klumpp *et al.*[1] to the equilibrium mixture (2; R = H) ⇌ (3; R = H),[4] we found that the reduction was not selective. Attempts to prepare (1; R = H) by selective catalytic reduction of the diene (2; R = H) proved equally unrewarding as might have been expected.[5]

Since methods which depended on the selectivity of reduction of the double bonds in the equilibrium mixture (2) ⇌ (3) seemed to present problems, we sought a more reliable synthesis of the 2-oxabicyclo[3.2.1]oct-3-ene system. The lactone (5) [6] seemed an appropriate starting material; however we did not obtain compound (1; R = H) by direct reduction with a variety of reducing agents. These experiments resulted either in non-reduction or in over-reduction to give the diol (6; R = H). The lactone (5) could be transesterified to afford the ester (7; R = H), and thence converted *via* the tetrahydropyranyl derivative (7; R = tetrahydropyranyl) into the alcohol (6; R = tetrahydropyranyl). Oxidation of this alcohol with Collins reagent yielded the aldehyde (8; R = tetrahydropyranyl), but attempts to convert this into the desired enol ether (1; R = H) were not successful.

To circumvent the foregoing problems, the lactone (5) was converted into the α-formyl-lactone (9). This rearranged readily and in good yield on treatment with 5% methanolic hydrogen chloride to give the ester (10; R = CO_2Me). This could be converted into a variety of 4-substituted 2-oxabicyclo[3.2.1]oct-3-enes. Reduction with lithium aluminium hydride gave the



alcohol (10; R = CH_2·OH), which could be oxidised with manganese dioxide to a compound with spectra compatible with the aldehyde structure (10; R = CHO). Hydrolysis of the ester (10; R = CO_2Me) yielded the

[1] G. W. Klumpp, J. W. F. Barnick, A. H. Veefkind, and F. Bickelhaupt, *Rec. Trav. Chim.*, 1969, **88**, 766.
[2] W. C. Agosta and D. K. Herron, *J. Amer. Chem. Soc.*, 1968, **90**, 7025.
[3] P. Barraclough, D.Phil. Thesis, Sussex, 1972.
[4] M. Rey and A. S. Dreiding, *Helv. Chim. Acta*, 1965, **48**, 1985.
[5] A. G. Cook, S. B. Herscher, D. J. Schultz, and J. A. Burke, *J. Org. Chem.*, 1970, **35**, 1550.
[6] J. Meinwald and E. Frauenglass, *J. Amer. Chem. Soc.*, 1960, **82**, 5235.

acid (10; R = CO_2H), decarboxylation of which afforded 2-oxabicyclo[3.2.1]oct-3-ene (1; R = H).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 237 instrument and u.v. spectra with a Unicam SP 800 spectrophotometer. N.m.r. spectra were determined by Mr. P. Dew using a Varian HA100 spectrometer and mass spectra with a Hitachi RMU-6 or A.E.I. MS9 instrument by Mr. A. Greenway. G.l.c. was performed by Mr. C. Simpson and his staff using a Pye–Unicam 104/64 instrument equipped with a flame ionisation detector. We thank Mr. and Mrs. A. G. Olney for microanalyses.

Reduction of the Lactone (5).—70% ' Red-al ' solution (R. N. Emanuel Ltd.; 3 g) in dry benzene (3 ml) was added over 15 min to a stirred solution of the lactone (5) [6] (400 mg) in dry benzene (5 ml). The mixture was stirred at room temperature overnight and the excess of ' Red-al ' was destroyed by addition of methanol, then water. The precipitated salts were filtered off and the benzene solution was washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield 2-(3-*hydroxycyclopentyl*)-*ethanol* (6; R = H) as an oil which was distilled; b.p. 92° at 0.1 mmHg; yield 150 mg; g.l.c. purity 99.1%, t_R 55 min (5 ft 5% Carbowax 20M column at 150 °C); $\nu_{max.}$ ($CHCl_3$) 3 365br cm^{-1} (OH); *m/e* 112 ($M^+ - H_2O$); τ ($CDCl_3$) 5.71br (1 H, s, H_A), 6.36 (2 H, t, *J* 6 Hz, CH_2·OH), 7.89 (1 H, s, OH, exchangeable in D_2O), and 7.72—8.88 (9 H, complex m).

Methyl 3-*Hydroxycyclopentylacetate* (7; R = H).—Methanolic 10% hydrogen chloride (50 ml) was added to a solution of the lactone (5) (10 g) in methanol (50 ml). The solution was heated at reflux for 5 h and the solvent was removed *in vacuo*. The residue was distilled at 92—94 °C and 1 mmHg to yield the *ester* (7; R = H) as an oil (8.9 g), g.l.c. purity 99.6%, t_R 22.5 min (5 ft 5% Carbowax 20M column at 150 °C); *m/e* 158 (Found: C, 60.95; H, 9.1. $C_8H_{14}O_3$ requires C, 60.75; H, 8.9%), $\nu_{max.}$ (film) 3 368br (OH) and 1 735 cm^{-1} (ester); τ ($CDCl_3$) 5.70br (1 H, s, H_A), 6.36 (3 H, s, CO_2·CH_3), 7.60 (2 H, s), 8.17 (1 H, s, exchangeable with D_2O,OH), and 7.6—8.8 (7 H, m).

Methyl 2-(3-*Tetrahydropyran-2-yloxycyclopentyl*)*acetate* (7; R = *tetrahydropyranyl*).—Dihydropyran (4.5 g), concentrated hydrochloric acid (4 drops), and the methyl ester (7; R = H) (8 g) were shaken vigorously and left at room temperature for 5 h. Potassium hydroxide (600 mg) was added; the mixture was shaken thoroughly and chloroform (100 ml) and water (10 ml) were added. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was distilled to yield (b.p. 72—74° at 0.2 mmHg) the *tetrahydropyranyl ether* as an oil (8.2 g) (Found: C, 64.8; H, 9.4. $C_{13}H_{22}O_4$ requires C, 64.45; H, 9.15%); *m/e* 242; $\nu_{max.}$ (film) 1 735 cm^{-1} (ester); τ ($CDCl_3$) 5.46br (1 H, s, H_A), 5.80 (1 H, t, *J* 6 Hz, OCHO), 6.38 (3 H, s, CO_2Me), 6.04—6.6 (2 H, CH_2O), 7.62 (2 H, s), and 7.65—8.8 (13 H, m).

2-(3-*Tetrahydropyran-2-yloxycyclopentyl*)*ethanol* (6; R = *tetrahydropyranyl*).—The ester (7; R = tetrahydropyranyl) (8.0 g) in dry diethyl ether (40 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.6 g) in dry diethyl ether (50 ml). The mixture was stirred overnight at room temperature and the excess of hydride was destroyed by addition of methanol, then water. The precipitated salts were filtered off and the aqueous layer was extracted with ether. The extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Distillation of the residue (b.p. 105 °C at 0.1 mmHg) yielded the *alcohol* as an oil (4.5 g) (Found: C, 67.35; H, 10.35. $C_{12}H_{22}O_3$ requires C, 67.25; H, 10.35%); *m/e* 214; $\nu_{max.}$ (film) 3 363br cm^{-1} (OH); τ ($CDCl_3$) 5.43br (1 H, s, H_A), 5.80 (1 H, quint., *J* 6 Hz, OC*H*O), 6.38 (2 H, t, *J* 6 Hz, CH_2·OH), 6.0—6.6 (2 H, m, CH_2OR), and 7.72—9.0 (15 H, m).

2-(3-*Tetrahydropyranyloxycyclopentyl*)*acetaldehyde* (8; R = *tetrahydropyranyl*).—Chromium oxide–pyridine complex (17 g) [7] was added in small portions over 20 min to a stirred solution of the alcohol (6; R = tetrahydropyranyl) (3.0 g) in dichloromethane (250 ml). The mixture was stirred for a further 4 h at room temperature and filtered. The filtrate was concentrated *in vacuo* and the black residue was distilled, yielding the aldehyde as a pale yellow liquid (1.2 g), b.p. 82° at 0.1 mmHg [*oxime* (Found: C, 63.0; H, 9.1; N, 6.35. $C_{12}H_{21}NO_3$ requires C, 63.4; H, 9.3; N, 6.15%)]; $\nu_{max.}$ (film) 1 722 cm^{-1} (CH=O); τ ($CDCl_3$) 0.24br (1 H, s, CHO), 5.40br (1 H, s, H_A), 5.74br (1 H, t, *J* 6 Hz, OCHO), 6.0—6.6 (2 H, m, CH_2·OR), and 7.4—8.80 (15 H, m); τ (oxime) ($CDCl_3$) 2.57 and 3.23 (1 H, 2 × t, *J* 7 Hz, *syn* and *anti* CH=N), 5.36br (1 H, s, H_A), 5.76br (1 H, t, OCHO), 6.0—6.6 (2 H, m, CH_2·OR), and 7.5—8.8 (15 H, m).

3-*Oxo*-2-*oxabicyclo*[3.2.1]*octane*-4-*carbaldehyde* (9).—Ethyl formate (12 g) and the lactone (5) (16 g) were dissolved in dry diethyl ether (250 ml) and stirred at room temperature for 2 days with small pieces of sodium metal (3.8 g). Water (70 ml) was carefully added and the mixture was stirred until two clear layers were observed. The aqueous layer was washed with chloroform and acidified with 5N-hydrochloric acid. The precipitated *solid* was filtered off, washed with water, and dried *in vacuo* (yield 10 g; m.p. 112—113°); it could be further purified by sublimation at 85 °C and 0.06 mmHg (Found: C, 62.5; H, 6.75. $C_8H_{10}O_3$ requires C, 62.3; H, 6.55%); $\nu_{max.}$ ($CHCl_3$) 1 673 cm^{-1} (conj. C=O), $\lambda_{max.}$ (MeOH) 247 nm (log ε 3.98), $\lambda_{max.}$ (NaOH–MeOH) 283 nm; *m/e* 154; τ ($CDCl_3$) −1.70 (1 H, d, *J* 11 Hz, OH, exchangeable with D_2O), 3.02 (1 H, d, *J* 11 Hz, H_X; br s after addition of D_2O), 5.12br (1 H, s, H-1), 7.16br (1 H, s, H-5), and 7.78—8.50 (6 H, m). The coupling of the hydrogen-bonded enolic OH and H_X was in keeping with expectation.[8]

Methyl 2-*Oxabicyclo*[3.2.1]*oct*-3-*ene*-4-*carboxylate* (10; R = CO_2Me).—Methanolic 10% hydrogen chloride (80 ml) was added to a solution of the α-formyl-lactone (9) (9.5 g) in methanol (80 ml) and the mixture was heated at 60 °C for 14 h. Sodium carbonate (5.0 g) was added and the suspension was diluted with water and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was distilled at 74—75° and 8.0 mmHg to give the *ester* as an oil (7.8 g); $\nu_{max.}$ (film) 1 708 cm^{-1} (C=O), $\lambda_{max.}$ (MeOH) 248 nm (log ε 4.13); *m/e* 168 (Found: C, 64.8; H, 7.45. $C_9H_{12}O_3$ requires C, 64.25; H, 7.2%); τ (CCl_4) 2.84 (1 H, s, H-3), 5.32br (1 H, s, H-1), 6.38 (3 H, s, CO_2Me), 7.04br (1 H, s, H-5), and 7.88—8.60 (6 H, m).

2-*Oxabicyclo*[3.2.1]*oct*-3-*en*-4-*ylmethanol* (10; R = CH_2·OH).—A solution of the ester (10; R = CO_2Me) (2.0 g) in dry diethyl ether (25 ml) was added over 20 min to a stirred suspension of lithium aluminium hydride (400 mg)

[7] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.

[8] E. W. Garbisch, *J. Amer. Soc.*, 1963, **85**, 1696.

in dry diethyl ether (25 ml). The suspension was stirred at room temperature for a further 3 h and the excess of hydride was destroyed by addition of methanol, then water. The inorganic salts were filtered off, the aqueous layer was extracted with ether, and the ether layers were dried (Na_2SO_4) and evaporated. The resulting oil (1.3 g) was unstable at room temperature but could be stored satisfactorily at −78 °C; *m/e* 140, $\nu_{max.}$ (film) 3 380 cm^{-1} (OH); τ ($CDCl_3$) 3.89 (1 H, s, H-3), 5.39br (1 H, s, H-1), 6.06 (2 H, s, CH_2·OH), 7.48br (1 H, t, *J* 4 Hz, H-5), and 7.84—8.6 (6 H, m).

2-*Oxabicyclo*[3.2.1]*oct*-3-*ene*-4-*carbaldehyde* (10; R = CHO).—The alcohol (10; R = CH_2·OH) (500 mg) and activated manganese dioxide (3.5 g) were stirred in reagent grade dichloromethane (25 ml) for 24 h at room temperature under nitrogen. The suspension was filtered and the solvent removed *in vacuo* to yield an oil which ran as one spot on t.l.c. (silica gel G; $CHCl_3$). Attempted distillation was accompanied by decomposition. The product (450 mg) showed $\nu_{max.}$ (film) 1 668 cm^{-1} (C=O), *m/e* 138, τ ($CDCl_3$) 0.86 (1 H, s, CH=O), 2.94 (1 H, s, H-3), 5.10br (1 H, s, H-1), 6.84br (1 H, s, H-5), and 7.80—8.60 (6 H, m).

2-*Oxabicyclo*[3.2.1]*oct*-3-*ene*-4-*carboxylic Acid* (10; R = CO_2H).—The methyl ester (10; R = CO_2Me) (7.50 g) was stirred at room temperature for 24 h with sodium hydroxide (3.0 g) in water (60 ml). The aqueous solution was washed with chloroform and acidified with 5N-hydrochloric acid. The precipitate was washed with water and dried *in vacuo* to yield the *acid* (4.0 g), m.p. 80—81°, which could be sublimed at 92 °C and 5 mmHg; $\nu_{max.}$ ($CHCl_3$) 1 668 cm^{-1} (C=O), $\lambda_{max.}$ (MeOH) 246 nm (log ε 4.10) (Found: C, 62.25; H, 6.55. $C_8H_{10}O_3$ requires C, 62.3; H, 6.55%), *m/e* 154; τ ($CDCl_3$) −0.58br (1 H, s, CO_2H, exchangeable with D_2O), 2.56 (1 H, s, H-3), 5.21br (1 H, s, H-1), 7.00br (1 H, s, H-5), and 7.7—8.5 (6 H, m).

2-*Oxabicyclo*[3.2.1]*oct*-3-*ene* (1; R = H).—The acid (10; R = CO_2H) (1.0 g) was heated at reflux for 3 h in redistilled quinoline (10 ml) containing copper powder (60 mg). The mixture was then distilled (short-path; receiver at −78 °C). At 1 mmHg an oil distilled over at room temperature (250 mg) which was shown to be 94% pure by g.l.c. (t_R 5.05 min; 5 ft 5% FFAP column at 100 °C; 6% quinoline present); *m/e* 110; $\nu_{max.}$ (film) 1 632 cm^{-1} (vinyl ether); τ ($CDCl_3$) 3.96 (1 H, d, *J* 5 Hz, H-3), 5.12 (1 H, t × d, *J* 5 and 2 Hz, H-4), 5.44br (1 H, s, H-1), and 7.69—8.70 (7 H, m).

One of us (P. B.) thanks the S.R.C. for a studentship.

[5/1292 *Received*, 30*th June*, 1975]