Aust. J. Chem., 1994, **47**, 1833–1841

Synthesis of Bridgehead-Substituted Bicyclo[2.2.1]heptanes. Radical Cyclization of an Oxime Ether and an α,β-Unsaturated Ester

Ernest W. Della[A,B] *and Andrew M. Knill*[A]

[A] School of Physical Sciences, Flinders University, Bedford Park, S.A. 5042.
[B] Author to whom correspondence should be addressed.

Abstract

The synthesis of bicyclo[2.2.1]heptanes with useful functionality at each bridgehead is achieved by radical cyclization of appropriately substituted 4-methylene- and 4-benzyloxyimino-cyclohexylmethyl radicals. The latter process, for example, leads to a bridgehead amine. Optimum yields are achieved when the reactions are conducted at 110° with slow addition of tributyltin hydride; under these conditions, the uncyclized isomer is either not detected, or formed in very small quantity. Production of a mixture of five- and six-membered cycloalkanones from similar treatment of the analogous 4-oxocyclohexylmethyl radicals reveals that the reaction is medicated by the corresponding 1-norbornyloxy radical.

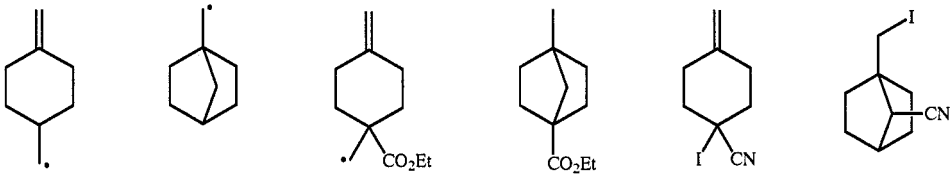
Introduction

Intramolecular radical cyclization is an important procedure for the synthesis of carbocyclic compounds.[1] We recently reported[2] that 5-*exo trig* cyclization of the 4-methylenecyclohexylmethyl radical (1) to give the bicyclic isomer (2) is a thermodynamically favourable process despite the introduction of strain associated with ring closure. In fact, the energy derived from formation of the new σ-bond more than compensates for the increase in strain in the new system and the loss of the π-bond. Kinetically, it was observed that the transformation (1) → (2) has an activation barrier of 53·5 kJ mol^{-1} which, as expected, is considerably higher than that determined for ring closure of the parent hex-5-enyl radical to the 1-methylcyclopentyl radical.[3,4] Nevertheless, by using modified 4-methylenecyclohexylmethyl radicals we were able to demonstrate that the process (1) → (2) has practical application for the synthesis of bridgehead-substituted bicyclo[2.2.1]heptanes. For example, it was found that the species (3) could be induced to cyclize and give the bicyclo[2.2.1]heptyl derivative (4) in excellent yield. Similarly, conversion of the iodide (5) into the isomer (6) was effected, essentially quantitatively, through an iodine-atom-transfer process initiated by $Me_3Sn^{\bullet}$ in catalytic quantity. We have now extended the procedure to the

[1] Grissom, J. W., and Klingberg, D., *J. Org. Chem.*, 1993, **58**, 6559, and references cited therein.
[2] Della, E. W., Knill, A. M., and Pigou, P. E., *J. Org. Chem.*, 1993, **58**, 2110.
[3] Beckwith, A. L. J., Easton, C. J., Lawrence, T., and Serelis, A. K., *Aust. J. Chem.*, 1983, **36**, 545.
[4] Spellmeyer, D. C., and Houk, K. N., *J. Org. Chem.*, 1987, **52**, 959.

Manuscript received 12 May 1994 0004-9425/94/101833$05.00

synthesis of other useful bicyclo[2.2.1]hept-1-yl derivatives, and report the results of those investigations.

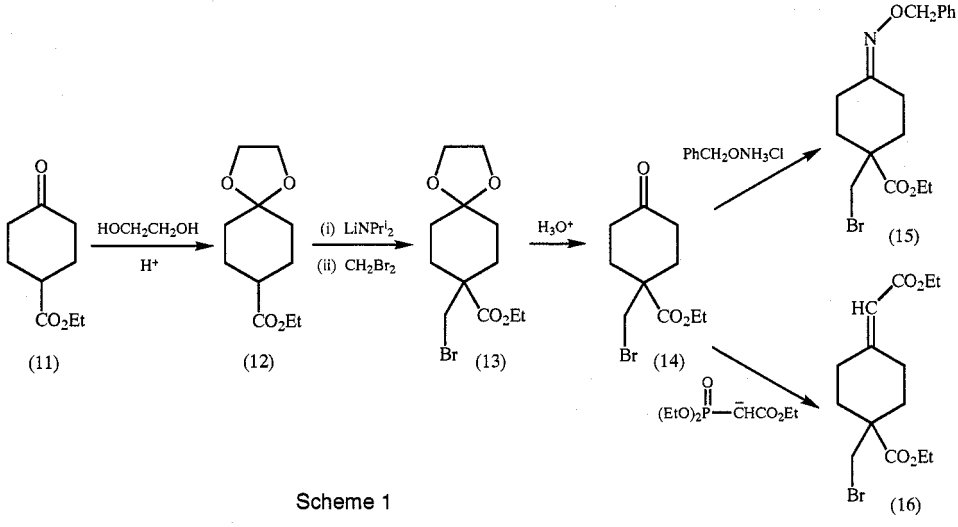


(1) (2) (3) (4) (5) (6)

Results and Discussion

Our principal objective has been to exploit the facility for ring closure displayed by radical (1) to generate bridgehead-substituted bicyclo[2.2.1]heptanes in which the functional groups either were themselves of inherent value or could be modified into other useful substitutents. Two additional radicals which were though to have considerable potential were the oxime ether (7) and the α,β-unsaturated ester (8), and the expectation was that cyclization of the kind described above would provide access to the bicyclo[2.2.1]hept-1-yl derivatives (9) and (10), respectively, by a relatively short sequence. These compounds are otherwise difficult to synthesize.

The required precursors (15) and (16) to the radicals (7) and (8) were synthesized in high yield from ethyl 4-oxocyclohexanecarboxylate (11), as depicted in Scheme 1, by standard transformations. It is noteworthy that conversion of the bromo ketone (14) into the target bromides (15) and (16) by treatment with the nucleophilic reagents occurs in high yield and is not complicated by the presence of the primary bromide because of its neopentyl-type arrangement.

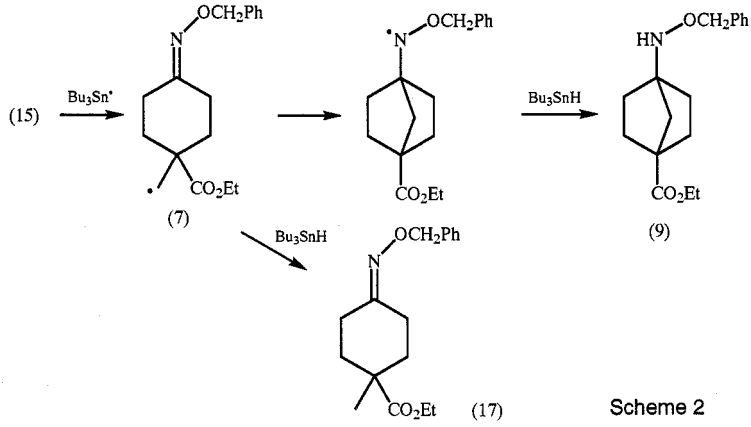


Scheme 1

Radical cyclization involving oxime ethers as acceptors was first reported by Corey and Pyne,[5] and has been observed subsequently on several other

[5] Corey, E. J., and Pyne, S. G., *Tetrahedron Lett.*, 1983, **24**, 2821.

occasions.[6–11] The radical (7), generated by treatment of the bromide (15) with tributyltin hydride in the presence of a catalytic quantity of azobisisobutyronitrile, was also observed to cyclize and could be induced to give optimum yields of the substituted bicyclic product (9) when the mixture was maintained at 110°C in boiling toluene during slow addition of the stannane over several hours (Scheme 2). As expected, the process is facilitated by the presence of the ester group at C 1; this enhances the yield of cyclized product by lowering the activation barrier in accordance with the Thorpe–Ingold Effect.[12] The amine (9) was accompanied by a small amount (ratio 9 : 1) of the uncyclized isomer (17). However, the desired compound could be separated easily from the reduced product by taking advantage of its basicity.



Scheme 2

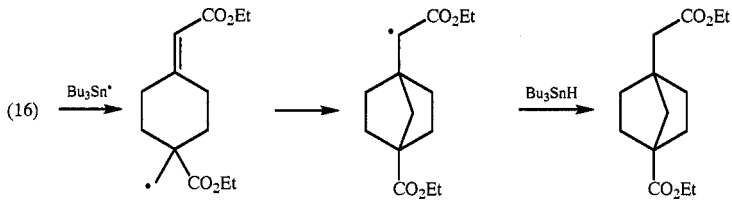
This route to (9) is performed readily and proceeds in high yield (82%, after purification by distillation) in five steps from the commercially available keto ester (11), and, since a variety of methods are available* for fission of the N–O bond, this represents an attractive procedure for the synthesis of bridgehead amines; at the same time, the other bridgehead position is occupited by a substituent which is amenable to further manipulation.

When treated under similar conditions, the bromide (16) afforded the bicyclo[2.2.1]heptane diester (10) in very good yield (79%) (Scheme 3). In this case the uncyclized isomer, which would have been derived by quenching of the primary radical (8) with tin hydride, was not detected among the products, a result suggesting that the stabilized nature of the cyclized radical (18) has the

* See reference 9 cited in ref. 10 above.

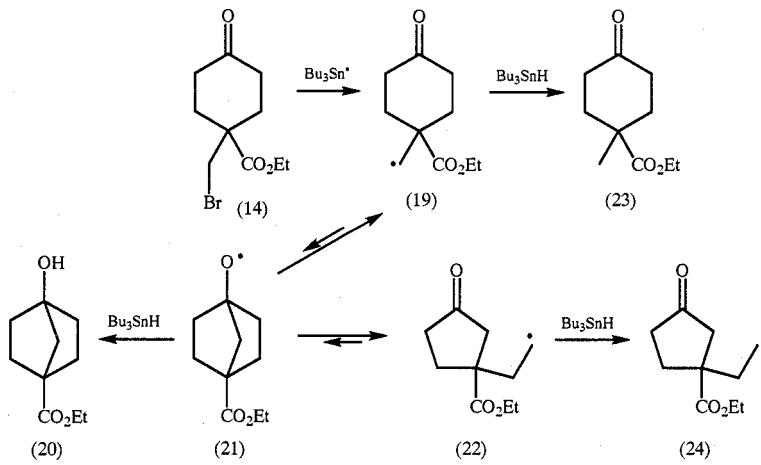
[6] Hart, D. F., and Seely, F. L., *J. Am. Chem. Soc.*, 1988, **110**, 1631.
[7] Bartlett, P. A., McLaren, K. L., and Ting, P. C., *J. Am. Chem. Soc.*, 1988, **110**, 1633.
[8] Marco-Contelles, J., Martinez-Grau, A., Bernabe, M., Martin, N., and Seoane, C., *Synlett*, 1991, 165.
[9] Enholm, E. J., Burroff, J. A., and Jaramillo, L. M., *Tetrahedron Lett.*, 1990, **31**, 3727.
[10] Booth, S. E., Jenkins, P. R., and Swain, C. J., *J. Chem. Soc., Chem. Commun.*, 1991, 1248.
[11] Marco-Contelles, J., Pozuelo, C., Jimeno, M. L., Martinez, L., and Martinez-Grau, A., *J. Org. Chem.*, 1992, **57**, 2625.
[12] Beesley, R. M., Ingold, K. C., and Thorpe, J. F., *J. Chem. Soc.*, 1915, **107**, 1080; Allinger, N. L., and Zalkow, V. J., *J. Org. Chem.*, 1960, **25**, 701.

effect of lowering the activation energy of its formation. The substance (10) has useful functionality at both bridgehead positions; the ester groups are distinguished by their rather different steric environments and it is expected that they could be elaborated independently as a result.



(8) (18) (10) Scheme 3

At this stage, we decided to include an analogous study of the bromo ketone (14), the precursor to the oxime ether (15) and α,β-unsaturated ester (16), in order to compare the effect of radical cyclization onto the C=O group in the derived radical (19) with that observed above in the connection with the C=N and C=C groups. Alkoxy radicals are high-energy species and, in a kinetic study of the radical cyclization of aldehydes and ketones, Beckwith and Hay[13] have shown that the position of equilibrium between open-chain and cyclic isomers favours the former. In the case of the radical (19), therefore, it was not expected that any significant quantity of the bicyclic alcohol (20) would be isolated because the concentration of its precursor (21) would be expected to be very small compared with that of the open-chain analogues (19) and (22). Accordingly, we were searching for a mixture of the ketones (23) and (24) in order to demonstrate that the bicyclo[2.2.1]hept-1-yloxy intermediate (21) had been produced (Scheme 4).

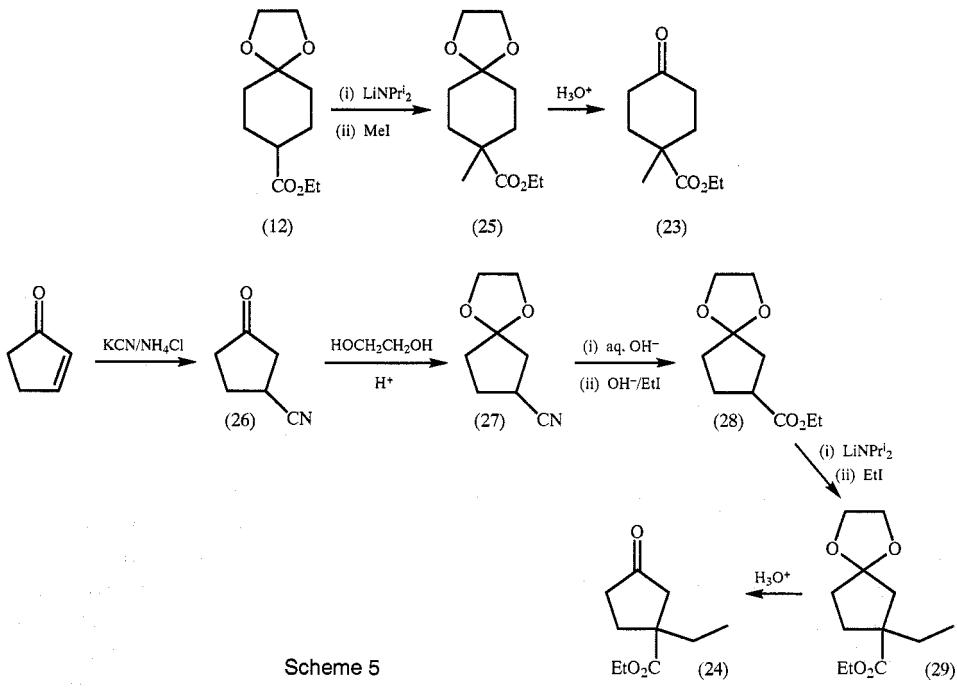


(14) (19) (23) (20) (21) (22) (24) Scheme 4

Treatment of the bromide (14) under the optimized conditions for cyclization specified above afforded a mixture (88:12) of the monocyclic keto esters (23) and (24); this showed that the interconversion (19) $\rightleftarrows$ (21) $\rightleftarrows$ (22) had, indeed,

[13] Beckwith, A. L. J., and Hay, B. P., *J. Am. Chem. Soc.*, 1989, **111**, 2674.

been established. As it proved impossible to separate the keto esters by gas chromatography, their presence in the reaction mixture was confirmed by comparison of its ^1H and ^{13}C n.m.r. spectra with those of authentic specimens. The latter were synthesized as illustrated (Scheme 5).



Scheme 5

In summary, cyclization of the imino- and methylene-substituted radicals (7) and (8) is seen to provide an excellent route to bicyclo[2.2.1]heptanes with malleable substituents at both bridgehead positions. The five-step sequence involved in each case proceeds in good yield and is readily performed from commercially available starting material (11).

Experimental

General spectral and chromatographic procedures were as previously described.[14] Microanalyses were performed by Chemical and Micro Analytical Services Pty Ltd, Victoria. Benzyloxyammonium chloride[15] and triethyl phosphonoacetate[16] were synthesized as reported.

Ethyl 4,4-Ethylenedioxycyclohexanecarboxylate (12)

A mixture of ethyl 4-oxocyclohexanecarboxylate (11) (10 g, 59 mmol), ethylene glycol (3·78 g, 61 mmol) and a catalytic amount of *p*-toluenesulfonic acid (30 mg) in benzene (20 ml) was heated under reflux for 5 h, a Dean and Stark water separator being used. The cooled mixture was washed successively with water (2×) and saturated sodium chloride solution, then dried ($MgSO_4$) and the solvent evaporated. Distillation yielded the title ketal (12) as a colourless liquid (11·4 g, 91%), b.p. (Kugelrohr) 120°/0·4 mm (lit.[17] 92–94°/0·01 mm).

[14] Della, E. W., and Gangodawila, H., *Aust. J. Chem.*, 1989, **42**, 1485.
[15] Fujii, T., Chin, C. W., and Yamada, S., *Chem. Pharm. Bull.*, 1967, **13**, 345.
[16] Kosolapoff, G. M., *J. Am. Chem. Soc.*, 1946, **68**, 1103.
[17] Musso, H., Naumann, K., and Grychtol, K., *Chem. Ber.*, 1967, **100**, 3614.

^{1}H n.m.r. δ 4·11, q, 2H; 3·96, s, 4H; 2·1–1·6, m, 9H; 1·25, t, 3H. ^{13}C n.m.r. δ 175·19, CO_2; 108·09, C 4; 64·3, OCH_2CH_2O; 60·26, $\mathbf{C}H_2CH_3$; 41·61, C 1; 33·75, C 3, C 5; 26·3, C 2, C 6; 14·23, $CH_2\mathbf{C}H_3$.

Ethyl 1-Bromomethyl-4,4-ethylenedioxycyclohexanecarboxylate (13)

A solution of lithium diisopropylamide was prepared by the addition of 2 M BuLi in pentane (20·3 ml, 41 mmol) followed by hexamethylphosphoric triamide (18 ml) to a solution of diisopropylamine (5·8 ml, 41 mmol) in dry tetrahydrofuran (100 ml) at −40° under nitrogen atmosphere. The mixture was cooled to −80° and ethyl 4,4-ethylenedioxycyclohexanecarboxylate (12) (8 g, 37 mmol) was added with the temperature maintained below −70° throughout the addition. After 20 min, dibromomethane (13·4 ml) was added and the mixture allowed to warm to room temperature. The mixture was poured into water, and extracted with pentane (3×). The combined extracts were washed successively with saturated sodium chloride solution (3×) before being dried ($MgSO_4$), and solvent evaporated. The residue solidified after standing for several days and was recrystallized from ether/hexane giving the *bromo ketal* (13) (9·77 g, 86%), m.p. 60–61° (Found: C, 46·9; H, 6·2. $C_{12}H_{19}BrO_4$ requires C 46·9; H, 6·2%). ^{1}H n.m.r. δ ($CDCl_3$) 4·2, q, 2H; 3·9, s, 4H; 3·48, s, 2H; 2·4–1·4, m, 8H; 1·26, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 173·19, CO_2; 108·1, C 4; 64·33, 64·27, OCH_2CH_2O; 61·03, $\mathbf{C}H_2CH_3$; 47·23, C 1; 40·09, CH_2Br; 31·62, 30·46, C 2, C 3, C 5, C 6; 14·25, $CH_2\mathbf{C}H_3$.

Ethyl 1-Bromomethyl-4-oxocyclohexanecarboxylate (14)

A solution of ethyl 1-bromomethyl-4,4-ethylenedioxycyclohexanecarboxylate (13) (6·0 g, 20 mmol) in acetone (20 ml) was treated 1 M sulfuric acid (80 ml), and allowed to stir at room temperature for 4 days. The crude mixture was extracted with CH_2Cl_2 (3×); the combned extracts were washed with saturated sodium chloride solution (2×), and then dried ($MgSO_4$). Removal of the solvent gave a yellow liquid which upon distillation afforded the title compound (14) as a colourless *oil* (4·39 g, 84%), b.p. (Kugelrohr) 100°/0·5 mm (Found: C, 45·6; H, 5·9. $C_{10}H_{15}BrO_3$ requires C, 45·7; H, 5·8%). ^{1}H n.m.r. δ ($CDCl_3$) 4·2, q, 2H; 3·6, s, 2H; 2·9–1·5, m, 8H; 1·33, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 209·67, C 4; 172·5, CO_2; 61·5, $\mathbf{C}H_2CH_3$; 47·11, C 1; 39·2, CH_2Br; 37·62, C 3, C 5; 32·25, C 2, C 6; 14·22, $CH_2\mathbf{C}H_3$.

Ethyl 4-Benzyloxyimino-1-bromomethylcyclohexanecarboxylate (15)

Benzyloxyammonium chloride (1·0 g, 6·3 mmol) was added to a stirred solution of ethyl 1-bromomethyl-4-oxocyclohexanecarboxylate (14) (1·5 g, 5·7 mmol) and pyridine (2·25 g) in dry ethanol (15 ml) at 0°. The mixture was allowed to warm to room temperature and left to stir for a further 30 min after which time it was taken up into ether, and washed successively with 10% acetic acid (3×), dilute sodium carbonate (2×) and saturated sodium chloride solution before being dried ($MgSO_4$). The solvent was removed to give a viscous oil (1·89 g, 90%), which was shown by spectroscopic analysis to consist of the *oxime ether* (15) only (Found: $M^{+\bullet}$, 369·0735, 367·0778. $C_{17}H_{22}BrNO_3$ requires $M^{+\bullet}$, 369·0764, 367·0784). ^{1}H n.m.r. δ ($CDCl_3$) 7·28, s, 5H; 5·05, s, 2H; 4·2, q, 2H; 3·45, s, 2H; 3·2–1·4, m, 8H; 1·26, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 172·77, CO_2; 158·02, C 4; 138·24, C *ipso*; 128·37, C *meta*; 127·95, C *ortho*; 127·69, C *para*; 75·36, $\mathbf{C}H_2Ph$; 61·26, $\mathbf{C}H_2CH_3$; 47·84, C 1; 39·66, CH_2Br; 32·77, 31·42, 28·18, 21·72, C 2, C 3, C 5, C 6; 14·36, $CH_2\mathbf{C}H_3$.

Ethyl 1-Bromomethyl-4-ethoxycarbonylmethylenecyclohexanecarboxylate (16)

Triethyl phosphonoacetate (1·89 g, 8·4 mmol) was added dropwise at 0° to a slurry of sodium hydride (0·21 g, 8·8 mmol) in dry 1,2-dimethoxyethane (15 ml). After the addition was complete the reaction mixture was stirred for 1 h at room temperature. The mixture was cooled to 0° and ethyl 1-bromomethyl-4-oxocyclohexanecarboxylate (2·0 g, 7·6 mmol) was added at such a rate that the temperature was maintained below 10°. After being stirred for a further 15 min at room temperature the mixture was taken up into water, and extracted

with ether (3×). The combined extracts were washed with saturated sodium chloride solution (2×), and dried ($MgSO_4$), and the solvent was evaporated. Distillation afforded the title compound (16) as a viscous liquid (2·3 g, 91%), b.p. (Kugelrohr) 150°/0·05 mm (Found: $M^{+\bullet}$–EtOH, 286·0220. $C_{14}H_{21}BrO_4$–EtOH requires *m/z* 286·0205). ^1H n.m.r. δ ($CDCl_3$) 5·66, s, 1H; 4·2, q, 2H; 4·08, q, 2H; 3·5, s, 2H; 2·7–1·4, m, 8H; 1·3, t, 3H; 1·25, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 172·81, 1-C=O; 166·08, C=CH**C**=O; 159·96, C4; 114·18, CH; 60·99, 59·40, $\mathbf{C}H_2CH_3$; 47·73, C1; 39·69, CH_2Br; 33·69, 33·53, 33·38, 25·57, C2, C3, C5, C6; 14·19, 14·17, $CH_2\mathbf{C}H_3$.

Ethyl 4-Benzyloxyaminobicyclo[2.2.1]heptane-1-carboxylate (9)

Tributyltin hydride (2·3 g, 8·1 mmol) in dry toluene (20 ml) containing a few crystals of azobisisobutyronitrile was slowly added over a period of 6 h to a solution of (15) (1·0 g, 2·7 mmol) in deoxygenated refluxing toluene (85 ml). The mixture was then cooled and methyl iodide (2 ml) was added before the solvent was removed under vacuum. The residue which was shown by ^1H n.m.r. analysis to consist predominantly of the cyclic amine (9) contaminated with what appeared to be the reduced oxime ether (17) (ratio 9:1) was taken up into ether, and washed with 5% HCl (4×). The acidic solution was washed once with hexane and then brought to pH 10 by addition of concentrated sodium hydroxide solution. Extraction with CH_2Cl_2 in the usual way afforded the *amine* (9) as a clear liquid (0·65 g, 83%) (Found: $M^{+\bullet}$, 289·1693. $C_{17}H_{23}NO_3$ requires $M^{+\bullet}$, 289·1678). ^1H n.m.r. δ ($CDCl_3$) 7·28, s, 5H, 5·22, s, 1H; 4·67, s, 2H; 4·1, q, 2H; 2·2–1·4, q, 10H; 1·21, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 175·47, CO_2; 138·0, C *ipso*; 128·37, C *meta*; 128·33, C *ortho*; 127·79, C *para*; 77·18, $\mathbf{C}H_2Ph$; 69·97, C4; 60·23, $\mathbf{C}H_2CH_3$; 50·49, C1; 44·18, C7; 32·81, C3, C5; 31·81, C2, C6; 14·28, $CH_2\mathbf{C}H_3$. The derived *hydrochloride*, (9).HCl, crystallized from dichloromethane/hexane as fine needles, m.p. 141–142° (Found: C, 62·4; H, 7·2; N, 3·9. $C_{17}H_{24}ClNO_3$ requires C, 62·7; H, 7·4; N, 4·3%).

Ethyl 4-Ethoxycarbonylmethylbicyclo[2.2.1]heptane-1-carboxylate (10)

Tributyltin hydride (0·67 g, 2·3 mmol) in dry toluene (15 ml) containing a few crystals of azobisisobutyronitrile was slowly added over a perod of 3 h to a solution of (16) (0·7 g, 2·1 mmol) in refluxing toluene (70 ml). After the reaction had gone to completion (gas chromatographic analysis), the mixture was cooled and methyl iodide (0·5 ml) was added. The solvent was removed under vacuum and the yellow residual liquid subjected to column chromatography (silica gel). The fraction eluted with ether/hexane was distilled yielding the *diester* (10) as a clear liquid (0·42 g, 79%) (Found: C, 66·0; H, 8·8. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%). ^1H n.m.r. δ ($CDCl_3$) 4·12, q, 4H; 2·48, s, 2H; 2·4–1·4, m, 10H; 1·24, t, 6H. ^{13}C n.m.r. δ ($CDCl_3$) 175·64, bridgehead C=O; 171·88, $CH_2\mathbf{C}$=O; 60·01, $\mathbf{C}H_2CH_3$; 52·1, C1; 46·63, $\mathbf{C}H_2CO_2$; 46·03, C4; 40·01, C7; 34·59, C2, C6; 33·57, C3, C5; 14·24, 14·16, $CH_2\mathbf{C}H_3$.

Treatment of Ethyl 1-Bromomethyl-4-oxocyclohexanecarboxylate (14) with Bu_3SnH

Tributyltin hydride (0·85 g, 2·9 mmol) in dry toluene (20 ml) containing a few crystals of azobisisobutyronitrile was slowly added over a period of 3 h to a solution of ethyl 1-bromomethyl-4-oxocyclohexanecarboxylate (14) (0·7 g, 2·7 mmol) in refluxing toluene (115 ml). After the reaction had gone to completion (gas chromatographic analysis), the mixture was cooled and methyl iodide (0·5 ml) was added. The solvent was removed under vacuum and the residue distilled to afford a mixture (88:12) of ethyl 1-methyl-4-oxocyclohexanecarboxylate (23) and ethyl 1-ethyl-3-oxocyclopentanecarboxylate (24) which were identified by comparison with authentic samples prepared below.

Ethyl 1-Methyl-4-oxocyclohexanecarboxylate (23)

A solution of lithium diisopropylamide was prepared by the addition of 1·7 M BuLi in pentane (4·6 ml, 7·7 mmol) followed by hexamethylphosphoric triamide (4·5 ml) to a solution of diisopropylamine (1·1 ml, 7·7 mmol) in dry tetrahydrofuran (15 ml) at −40° under a nitrogen atmosphere. The mixture was cooled to −80° and ethyl 4,4-ethylenedioxycyclohexanecarboxylate

(12) (1·5 g, 7·0 mmol) was added so that the temperature was maintained below −70° throughout the addition. After 20 min, methyl iodide (2·2 ml) was added and the mixture allowed to warm to room temperature before being poured into water, and extracted with pentane (3×). The combined extracts were washed successively with saturated sodium chloride solution (3×) before being dried ($MgSO_4$) and evaporated giving *ethyl 4,4-ethylenedioxy-1-methylcyclohexanecarboxylate* (25) (1·32 g, 82%), b.p. (Kugelrohr) 95°/0·4 mm (Found: $M^{+\bullet}$, 228·1342. $C_{12}H_{20}O_4$ requires $M^{+\bullet}$, 228·1362). ^1H n.m.r. δ ($CDCl_3$) 4·12, q, 2H; 3·9, s, 4H; 2·3–1·4, m, 8H; 1·25, t, 3H, 1·18, s, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 176·67, CO_2; 108·26, C 4; 64·05, OCH_2CH_2O; 60·12, $\mathbf{C}H_2CH_3$; 42·14, C 1; 32·75, C 2, C 6; 31·95, C 3, C 5; 25·84, CH_3; 14·07, $CH_2\mathbf{C}H_3$. A solution of the ketal (25) (0·9 g, 3·9 mmol) in acetone (10 ml) was treated with 1 M sulfuric acid (40 ml) with stirring at room temperature for 24 h. The mixture was extracted with CH_2Cl_2 (3×); the combined extracts were washed with saturated sodium chloride solution (2×), and dried ($MgSO_4$). Removal of the solvent gave a yellow liquid which upon distillation afforded the *title compound* (23) (0·66 g, 91%), b.p. (Kugelrohr) 95°/0·8 mm (Found: C, 45·6; H, 5·9. $C_{10}H_{16}O_3$ requires C, 45·7; H, 5·8%). ^1H n.m.r. δ ($CDCl_3$) 4·27, q, 2H; 2·7–1·5, m, 8H; 1·28, t, 3H; 1·28, s, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 210·67, C 4; 176·1, CO_2; 60·82, CH_2CH_3; 42·39, C 1; 38·45, C 3, C 5; 35·2, C 2, C 6; 25·72, CH_3; 14·29, CH_2CH_3.

3-Oxocyclopentanecarbonitrile (26)

Cyclopent-2-enone (10 g, 0·122 mol) was dissolved in acetonitrile/water (9:1 v/v) (500 ml) containing KCN (15·8 g, 0·244 mmol) and NH_4Cl (9·8 g, 0·183 mol), and the mixture stirred at room temperature for 24 h. The mixture was poured into water, and extracted with CH_2Cl_2 (3×). The combined extracts were washed once with saturated sodium chloride solution, and solvent was removed to give a yellow liquid. Distillation (110°/1·5 mm) afforded the title ketone (26) as a clear liquid (11·1 g, 83%) whose i.r. and ^1H n.m.r. data were consistent with those reported.[18]

3,3-Ethylenedioxycyclopentanecarbonitrile (27)

3-Oxocyclopentanecarbonitrile (26) (5 g, 46 mmol), ethylene glycol (3·13 g, 50 mmol) and a catalytic amount of *p*-toluenesulfonic acid (23 mg) in benzene (20 ml) were heated under reflux for 2·5 h, a Dean and Stark water separator being used. The cooled mixture was washed successively with water (2×) and saturated sodium chloride solution, then dried ($MgSO_4$) and the solvent evaporated. Distillation yielded the title *ketal* (27) (5·96 g, 85%), b.p. (Kugelrohr) 100°/0·7 mm (Found: C, 62·7; H, 7·4; N, 9·1. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%). ^1H n.m.r. δ 3·91, s, 4H; 3·15–2·6, m, 1H; 2·5–1·7, m, 6H. ^{13}C n.m.r. δ ($CDCl_3$) 122·26, CN; 116·05, C 1; 64·71, 64·45, OCH_2CH_2O; 40·16, C 2; 34·95, C 5; 28·27, C 3; 25·5, C 4.

Ethyl 3,3-Ethylenedioxycyclopentanecarboxylate (28)

3,3-Ethylenedioxycyclopentanecarbonitrile (27) (5·6 g, 3·7 mmol) and a solution of 10% (w/w) NaOH (30 ml) was heated under reflux until the loss of ammonia from the reaction has ceased (*c.* 3 h). The reaction mixture was acidified to pH 2 and extracted with ether (5×). The combined extracts were washed with saturated sodium chloride (2×), and dried ($MgSO_4$). Removal of the solvent gave a clear viscous oil (6·2 g, 98%). ^1H n.m.r. δ 9·8, s, 1H; 3·85, s, 4H; 3·3–1·65, m, 7H. ^{13}C n.m.r. δ ($CDCl_3$) 180·83, C=O; 117·15, C 3; 64·49, 64·22, OCH_2CH_2O; 41·17, C 2; 38·70, C 1; 35·28, C 4; 26·79, C 5. A portion (1·68 g, 9·8 mmol) was dissolved in hexamethylphosphoric triamide (25 ml), and neutralized by addition of aqueous NaOH (2·4 ml, 25% solution). Ethyl iodide (5 g, 30 mmol) was added; the mixture was stirred for 1 h, then poured into water, and extracted with hexane (3×). The combined extracts were washed with saturated sodium chloride solution (2×), and dried ($MgSO_4$); after this the solvent was removed. Distillation of the residue afforded the *title compound* (28) (1·5 g, 77%), b.p. (Kugelrohr) 85°/0·5 mm (Found: C, 59·7; H, 8·2. $C_{10}H_{16}O_4$ requires C, 60·0;

[18] Farcasiu, D., Schleyer, R., and Ledlie, D. B., *J. Org. Chem.*, 1973, **38**, 3455.

H, 8·1%). ^{1}H n.m.r. δ 4·1, q, 2H; 3·87, s, 4H; 3·2–1·7, m, 7H; 1·22 t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 175·02, C=O; 117·19, C 3; 64·57, 64·24, OCH_2CH_2O; 60·4, $\mathbf{C}H_2CH_3$; 41·5, C 2; 39·05, C 1; 35·41, C 4; 26·97, C 5; 14·25, $CH_2\mathbf{C}H_3$.

Ethyl 1-Ethyl-3-oxocyclopentanecarboxylate (24)

A solution of lithium diisopropylamide was prepared by the addition of 1·8 M BuLi in pentane (3·05 ml, 5·5 mmol) followed by hexamethylphosphoric triamide (3 ml) to a solution of diisopropylamine (0·78 ml, 5·5 mmol) in dry tetrahydrofuran (15 ml) at −40° under a nitrogen atmosphere. The mixture was cooled to −80° and ethyl 3,3-ethylenedioxycyclopentanecarboxylate (1 g, 5 mmol) was added while the temperature was maintained below −70° throughout the addition. After 20 min, ethyl iodide (1·6 ml) was added and the mixture allowed to warm to room temperature before being poured into water, and extracted with pentane (3×). The combined extracts were washed successively with saturated sodium chloride solution (3×) before being dried ($MgSO_4$) and evaporated. Distillation afforded the *ester ketal* (29) (0·96 g, 84%), b.p. (Kugelrohr) 90°/0·4 mm (Found: $M^{+\bullet}$, 228·1333. $C_{12}H_{20}O_4$ requires $M^{+\bullet}$, 228·1362). ^{1}H n.m.r. δ 4·16, q, 2H; 3·86, s, 4H; 2·6–1·4, m, 8H; 1·23, t, 3H; 0·91, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 176·58, CO_2; 117·03, C 3; 64·19, OCH_2CH_2O; 60·41; $O\mathbf{C}H_2CH_3$; 52·32, C 1; 44·61, C 2; 35·19, C 4; 32·68, 32·28, $\mathbf{C}H_2CH_3$, C 5; 14·22, $OCH_2\mathbf{C}H_3$; 9·73, $CH_2\mathbf{C}H_3$. To a solution of the ester (29) (0·7 g, 3·1 mmol) in acetone (7 ml) was added 1 M sulfuric acid (30 ml), and the mixture allowed to stir at room temperature for 24 h. The mixture was extracted with CH_2Cl_2 (3×); the combined extracts were washed with saturated sodium chloride solution (2×), and dried ($MgSO_4$). Removal of the solvent gave a clear liquid which upon distillation afforded the *ketone* (24) (0·53 g, 94%), b.p. (Kugelrohr) 90°/0·7 mm (Found: C, 65·2; H, 9·0. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·8%). ^{1}H n.m.r. δ ($CDCl_3$) 4·2, q, 2H; 3·0–1·5, m, 8H; 1·27, t, 3H; 0·91, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 216·65, C 3; 175·58, CO_2; 60·95, $O\mathbf{C}H_2CH_3$; 51·61, C 1; 46·91, C 2; 36·77, C 4; 32·33, C 5; 31·2, $\mathbf{C}H_2CH_3$; 14·22, $OCH_2\mathbf{C}H_3$; 9·88, $CH_2\mathbf{C}H_3$.

Acknowledgment

We thank the Australian Research Council for financial support of this work.