Bridged Ring Systems. Part 20.[1] A Synthesis of 2,5-Dimethylcyclohept-4-enone

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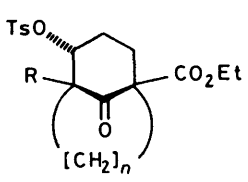
Diethyl 2,5-dimethylcyclohept-4-ene-1,1-dicarboxylate has been synthesised from ethyl 3-methyl-2-oxocyclopentane-1-carboxylate *via* a bicyclic tosyloxy-ketone intermediate. Only one of the ester functions is hydrolysed by alkali and the resulting half-ester has been converted into the title ketone. A new fragmentation reaction of an axial tosyloxy-ketone is reported.

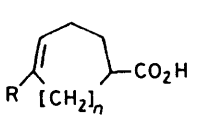
In earlier publications [2-4] we have demonstrated that the equatorial tosyloxy-ketones (1a—c) undergo a facile fragmentation on treatment with NaOEt, affording *cis*-cycloalk-4-ene-1,1-diesters and thence the cycloalkenecarboxylic acids (2a—c), in what promises to be a general synthetic route. Recently others [5] have employed the method in a synthetic approach to the ophiobolins but its scope and limitations have not been adequately tested. We report here on some further investigations in this field.

RESULTS AND DISCUSSION

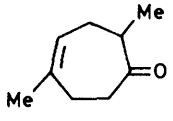
As part of another project, the dimethylcycloheptenone (3) was required as an intermediate and has been synthesised as follows. The mixture of keto-alcohols (4)



(1) a; R = H; n = 2
b; R = Me; n = 3
c; R = Me; n = 4



(2)



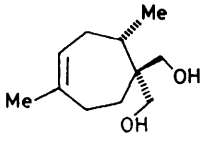
(3)

was prepared from ethyl 3-methyl-2-oxocyclopentane-1-carboxylate [6] and crotonaldehyde and converted to the mixture of toluene-*p*-sulphonates (5). These were separated and identified by n.m.r. The equatorial *p*-toluenesulphonates (1 H, δ 4.5, $W_{\frac{1}{2}}$ 16 Hz) and its axial isomer (1 H, δ 4.68, $W_{\frac{1}{2}}$ 6 Hz) showed, *inter alia*, methyl doublets at δ 0.95 (J 7 Hz) and 0.91 (J 7 Hz) respectively and the near identity of these chemical shifts indicates [7] that the methyl groups are equatorial in both epimers. The equatorial toluene-*p*-sulphonate (5a) was smoothly converted to the *gem*-diester (6) by mild treatment with NaOEt, whilst under identical conditions the axial epimer (5b) was recovered in high yield.

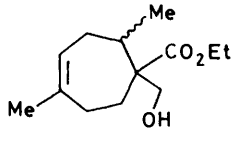
The inertness of the axial epimer is not unexpected, for compounds of this type are stereoelectronically incapable of a facile (concerted) fragmentation.[4] It is therefore of interest to report that when KOH was used in place of NaOEt, the axial toluene-*p*-sulphonate (5b) afforded the acid (9) in excellent yield, together with a small amount of the corresponding ester (8). These products must arise *via* (10) by a *syn*-periplanar fragmentation.

Surprisingly, on prolonged boiling with ethanolic alkali, the diester (6) yielded only the half-ester (7). The structure of the latter was confirmed by decarboxylation to (8) which was readily hydrolysed to the acid (9); its configuration (7) was determined by treating the toluene-*p*-sulphonate with one equivalent of NaOH. The resulting half-ester, in which the free CO_2H must be *trans* to the adjacent methyl group [(11) ⟶ (8)], was shown to be identical with the hydrolysis product by comparison of their methyl esters. It is therefore the axial ester function in (6) which survives under these reaction conditions. In contrast, the simple diester (12) was completely hydrolysed at room temperature.[3] An adjacent methyl group exerts no such profound effect in the analogous cyclohexane series. The 2-methyl-, 2-phenyl-, and even 2,2,4-trimethyl-cyclohexane-1,1-dicarboxylic acids are all formed from their diesters under fairly mild conditions.[8] On the other hand, *both* ester functions in (6) were readily reduced by $LiAlH_4$, yielding the diol (13). Even under competitive conditions, *i.e.* using insufficient reducing agent, the reaction product was a mixture of (6), (13), and (14).

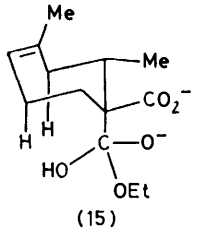
To interpret these observations, we are compelled to postulate; (*i*) that in the cycloheptene series, 1,3-nonbonded interactions are so severe that the tetrahedral



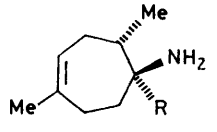
(13)



(14)



(15)

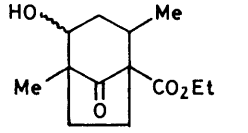


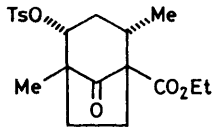
(16), R = CO_2Et
(17); R = CH_2OH

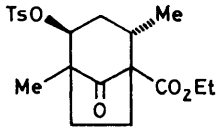
intermediate (15) is sterically disallowed; and more surprisingly, (*ii*) that this diester is locked in one conformation. The facile hydride reduction of both esters,

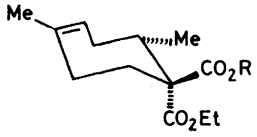
even under competitive conditions, is probably achieved *via* an intermediate aluminohydride complex, by an intramolecular delivery mechanism.

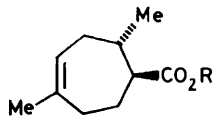
A direct conversion of (9) to (3) could not be achieved and the ketone was finally prepared, in very low yield, by a circuitous route. The half-ester (7) was converted to (16) by Curtius degradation and the latter reduced to the amino-alcohol (17) which on oxidative cleavage gave the ketone (3).

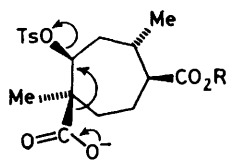

(4)

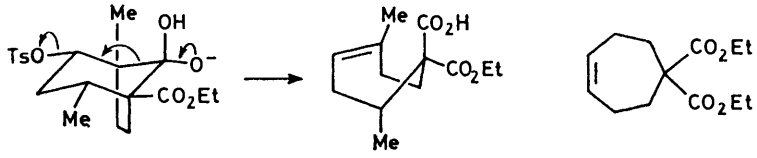

(5a)


(5b)


(6); R = Et
(7); R = H


(8); R = Et
(9); R = H


(10); R = H or Et


(11) (7) (12)

EXPERIMENTAL

Ethyl 2,5-*Dimethyl*-4-*hydroxy*-8-*oxobicyclo*[3.2.1]*octane*-1-*carboxylate* (4).—A mixture of ethyl 3-methyl-2-oxocyclopentane-1-carboxylate (13.3 g) and crotonaldehyde (6 g), cooled to 0 °C, was added dropwise during 1 h to Na (0.1 g) in dry ethanol (50 ml) at −70 °C. The cooling bath was then removed, and stirring continued for 2 h. The solution was neutralised with glacial acetic acid, and solvent removed under reduced pressure. The residue was taken up in ether, washed, dried, and concentrated to yield (4), b.p. 165—167 °C at 0.4 mmHg (14.0 g, 75%) (Found: C, 64.75; H, 8.45. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%); $\nu_{max.}$ 3 630, 3 400—3 570, 1 760, and 1 735 cm^{-1}; δ 0.9 (d), 1.02 (s); *m/e* 240.

Toluene-p-*sulphonates* (5).—A solution of toluene-*p*-sulphonyl chloride (18.5 g) in dry pyridine (75 ml) was added with stirring to the mixture of alcohols (4) (15.5 g) at 0 °C, and stirred at room temperature for 4 d. The reaction mixture was then poured on to ice, extracted into ethyl acetate, washed, and evaporated to dryness. The crude oily product (19.8 g) was separated by fractional crystallisation (EtOH) into the *axial toluene*-p-*sulphonate* (5b), (3.1 g), m.p. 161—162 °C (Found: C, 60.90; H, 6.50. $C_{20}H_{26}O_6S$ requires C, 60.90; H, 6.46%); δ 4.68 ($W_{\frac{1}{2}}$ 6 Hz): and the *equatorial toluene*-p-*sulphonate* (5a) (6.2 g), m.p. 81—82 °C (Found: C, 61.06; H, 6.44. $C_{20}H_{26}O_6S$ requires C, 60.9; H, 6.64%); δ 4.5 ($W_{\frac{1}{2}}$ 16 Hz). Both epimers showed ν 1 765 and 1 735 cm^{-1}.

Diethyl 2,5-*Dimethylcyclohept*-4-*ene*-1,1-*dicarboxylate* (6).—The equatorial toluene-*p*-sulphonate (5 g) in dry ethanol (50 ml) was added dropwise during 10 min to a solution of sodium ethoxide [from sodium (0.5 g) in ethanol (60 ml)] at 60 °C. The mixture was stirred at reflux for 30 min, then cooled and poured into ice–water (50 ml). After neutralisation, the bulk of the solvent was removed *in vacuo*, and the residue was extracted into ether, washed, and solvent evaporated off to give the *diester* (6), b.p. 110—112 °C at 0.3 mmHg (2.81 g, 83%) (Found: C, 66.88; H, 8.83. $C_{15}H_{24}O_4$ requires C, 67.14; H, 9.01%); *m/e* 268; ν 1 735 cm^{-1}; δ 0.85 (d, 3 H), 1.23 (t, 6 H), 1.67 (s, 3 H), and 5.34 (br s, 1 H).

2,5-*Dimethylcyclohept*-4-*ene*-1-*carboxylic Acid* (9).—(*a*) The half-ester (1.1 g) in dry pyridine (10 ml) was boiled under reflux for 4 h. The solvent was then removed and the residue, in ether, was washed and concentrated to give the *ester* (8) (0.64 g, 72%), b.p. 85—90 °C at 0.25 mmHg (Found: C, 72.85; H, 10.15. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%); *m/e* 196; ν 1 738 cm^{-1}; δ 0.87 (d, 3 H), 1.70 (s, 3 H), and 5.5 (m, 1 H).

The ester (0.615 g) and KOH (0.28 g) in MeOH (25 ml) and H_2O (3 ml) was boiled for 16 h. The usual work-up gave the *acid* (9) (0.43 g), b.p. 120—124 °C at 0.35 mmHg (Found: H, 71.42; H, 9.48. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%); *m/e* 168; $\nu_{max.}$ 3 400—2 400 and 1 708 cm^{-1}; δ 0.93 (d, 3 H), 1.70 (s, 3 H), 5.43 (m, 1 H), and 12.01 (s, 1 H, exchangeable with D_2O).

(*b*) The axial toluene-*p*-sulphonate (5b) (4 g) and KOH (3.92 g) in ethanol (150 ml) were refluxed for 16 h. Most of the solvent was then removed under reduced pressure, water (100 ml) was added, and the resulting solution was extracted with ether. The organic extract yielded, on evaporation, the ethyl ester (8) (0.99 g), showing the spectro-

scopic features described in (*a*). The aqueous portion was acidified and re-extracted with ether, yielding the acid (9) (1.54 g), spectroscopically identical with the product above.

Half-ester (7).—(*a*) A solution of the diester (2.1 g) and KOH (1.1 g) in ethanol (10 ml) was refluxed for 16 h. After cooling, the solvent was removed under reduced pressure and the residue was taken up in water (30 ml). Any unreacted diester was removed by washing with ether, and the aqueous layer was acidified, extracted into ether, washed, and concentrated to yield the *acid-ester* (1.34 g, 71%) as a yellow oil, b.p. 133—136 °C at 0.25 mmHg (Found: C, 65.0; H, 8.4. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%); *m/e* 196 (*P* − 44); $\nu_{max.}$ 3 400—2 400, 1 740, and 1 708 cm^{-1}; δ 0.9 (d, 3 H), 1.7 (d, 3 H), 5.37 (br s, 1 H), and 11.2 (s, 1 H, exchangeable with D_2O), as well as ethyl ester signals. The product of methylation (CH_2N_2) showed a single peak on g.l.c., retention time 21.5 min on 10% APL at 150 °C, flow rate 60 ml min^{-1}. Hydrolysis by KOH in aqueous dioxan for 16 h yielded the same product (7).

(*b*) The equatorial toluene-*p*-sulphonate (5a) (0.2 g) in dioxan (5 ml) was added to KOH (50 mg) in water (1 ml) and refluxed for 30 min. The solution was cooled, acidified, extracted into ether, and then washed and evaporated to dryness. The resulting half-ester (0.11 g) was identified by comparison of its i.r. and n.m.r. spectra. After methylation (CH_2N_2) the product showed a single peak on g.l.c., retention time 21.5 min on 10% APL at 150 °C.

Lithium Aluminium Hydride Reduction.—(*a*) The diester (6) (100 mg, 0.37 mmol) in dry ether (5 ml) was added slowly to a slurry of $LiAlH_4$ (15 mg, 0.39 mmol) in dry ether (5 ml) and stirred under N_2 for 4 h at 15 °C. After addition of water (5 ml) and dilute HCl (1 ml) the granular solid was filtered off and washed with ether, and the combined ethereal solutions were washed and solvent evaporated off to yield the *diol* (13) (61 mg, 89%), m.p. 89—90 °C (benzene) (Found: C ,71.50; H, 10.60. $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.94%); *m/e* 184; $\nu_{max.}$ 3 625 and 3 260—2 740 cm^{-1}; δ 5.30 (m, 1 H) and 3.12 (m, 2 H, exchangeable with D_2O).

(*b*) Using diester (100 mg) and $LiAlH_4$ (8 mg, 0.21 mmol) as above, but stirring for 16 h, the oily product (90 mg) was separated by preparative t.l.c. into three bands. The least polar corresponded to starting diester, the most polar corresponded to the above diol and the middle band (22 mg) was an oil which had ν 3 600—2 400 and 1 735 cm^{-1}; δ 1.23 (t, 3 H), 4.20 (q, 2 H), 5.49 (m, 1 H), and 6.42 (m, 1 H, exchangeable with D_2O). This was assumed to be the hydroxy-ester (14).

2,5-Dimethylcyclohept-4-en-1-one (3).—The half-ester (7) (5 g) in benzene (25 ml) was treated with thionyl chloride (2.2 ml), refluxed for 2 h, and then concentrated *in vacuo* to yield crude acid chloride (4.8 g), $\nu_{max.}$ 1 800 and 1 735 cm^{-1}. The product in acetone (25 ml) was treated with sodium azide (1.3 g) in water (5 ml), stirred for 2 h, then flooded with water and extracted into benzene. The benzene solution was washed and concentrated to yield crude azide-ester (ν 2 130 and 1 735 cm^{-1}) which was refluxed in benzene (25 ml). After 1.5 h, the azide absorption was replaced by the isocyanate peak (2 270 cm^{-1}) and solvent was removed, yielding crude isocyanate (2.95 g), which was refluxed for 30 min, with KOH (2 g) in methanol (80 ml) and water (6 ml). The mixture was flooded with water and extracted with ether. On work-up, the ether extract afforded non-acidic material (1.4 g), consisting of two main components (g.l.c.) retention times 14.2 and 23.0 min on 1% SE 30 at 100 °C, flow rate 55 ml min^{-1}. The former showed *m/e* 211 and was shown to be the amino-ester (16) by fragmentation peaks at *m/e* 194, 138, and 121. A sample, isolated by preparative t.l.c. in 30% EtOAc–light petroleum, showed $\nu_{max.}(CCl_4)$ 3 440, 3 400, and 1 734 cm^{-1}; δ 0.08 (d, 3 H), 1.26 (t, 3 H), 1.7 (br s, 3 H), 4.2 (q, 2 H), and 5.5 (br s, 1 H), consistent with (16).

The amino-ester (580 mg) in dry ether (12 ml) was added to $LiAlH_4$ (250 mg) in dry ether (12 ml) and stirred overnight under N_2. Work-up with saturated Na_2SO_4 gave the ether-soluble amino-alcohol (17); $\nu_{max.}$ *ca.* 3 500 cm^{-1} (broad), but no C=O absorption. Sodium metaperiodate (200 mg) in water (4 ml) was added to a solution of the amino-alcohol (150 mg) in 10 ml methanol and stirred for 24 h at room temperature. The solution was flooded with water, extracted with ether, and the extract was washed and evaporated to give a volatile oil (90 mg), comprising one major component which was separated by preparative t.l.c. The cycloheptenone (3) had a retention time of 29.4 min on 7% F60/1% Z at 75 °C, flow rate 50 ml min^{-1}; $\nu_{max.}$ (CCl_4) 1 710; δ 1.05 (d, 3 H, *J* 6 Hz); 1.73 (s), and 5.5 (m). It was characterised as its 2,4-dinitrophenylhydrazone, m.p. 116—117 °C (ethanol) (Found: 3, 56.60; H, 5.86; N, 17.71. $C_{15}H_{18}N_4O_4$ requires C, 56.6; H, 5.70; N, 17.60%).

Microanalyses were carried out by Mrs. W. Harkness and her staff, mass spectra were determined by Mr. A. Ritchie, and ^1H n.m.r. spectra by Mr. J. Gall. Two of us (H. L. B. and J.O'D) thank the Carnegie Trust for the Universities of Scotland, and the S.R.C., respectively, for financial support.

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