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PREPARATION AND OXIDATION OF 3-METHYLENE-, 3-OXO- AND 3-HYDROXY-BICYCLO[2,2,1]HEPTANE-2, 6-CARBOLACTONES

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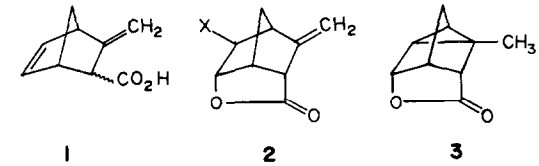
Abstract—3-methylenebicyclo[2,2,1]heptane-2,6-carbolactone (previously incorrectly claimed) has now been prepared and converted to the 3-oxo-lactone. Some 3-hydroxy-bicyclo-[2,2,1]heptane-2,6-carbolactones have been prepared and their rates of oxidation with chromic acid determined. The results do not support a theory about the mechanism of oxidation, involving a dipolar interaction from the lactone.

The recent statement by Ranganathan *et al.*[1] that a review is in preparation on bicyclo[2,2,1]heptane-2,6-lactones quoting our work[2] prompts us to record our current findings which extend our earlier conclusions,[2,3] and those of Ranganathan *et al.*[4]



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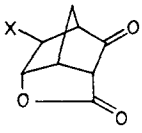

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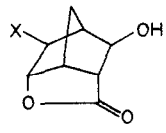

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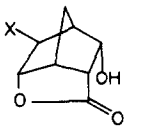

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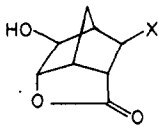

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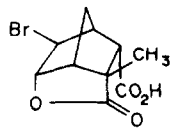

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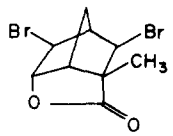

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Iodolactonisation of 3-methylenebicyclo[2,2,1]hept-5-enecarboxylic acid (**1**) gives 6-hydroxy-5-iodo-3-methylene-bicyclo[2,2,1]hept-5-ene carboxylic acid 2,6-lactone (**2**, X = I). This lack of rearrangement is characteristic in this system only of iodolactonisation,[5-7] in contrast simple acid catalysed lactonisation gives[2,6] nortricyclene (e.g. **3**).

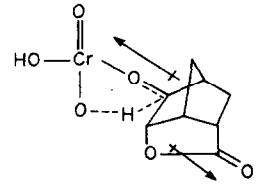
Dehalogenation of **1** gives the methylene-lactone **2**(X = H). This structure was originally[8] incorrectly ascribed to the compound which was shown[2] to be **3**. Oxidation of this with ruthenium tetroxide gives the oxo-lactone (**4**, X = H) which has been independently synthesised[4] by oxidation of the *exo*-hydroxy compound (**5**, X = H). Reduction of the oxo-lactone (**4**, X = H) gives the *endo*-hydroxy-lactone (**6**, X = H). Rates of oxidation by chromic acid of these and related compounds are given in Table 1.

These results permit for the first time a test of the

Table 1. Rates of oxidation of hydroxybicyclo[2,2,1]heptane carbolactones by 5×10^{-4} M-chromic acid in 4×10^{-2} M-perchloric acid at 31°

Compound	Rate $l.mol.min.^{-1}$	K_{rel}
3-oxo (4, X = H)	0.22	0.54
3-exo-OH (5, X = H)	1.13	2.75
3-endo-OH (6, X = H)	4.65	11.3
5-exo-OH (7, X = H)	0.41	1.00
5-exo-Br-3-exo-OH (5, X = Br)	0.49	1.20
3-exo-Br-5-exo-OH (7, X = Br)	0.26	0.638

proposal[9] that the very slow oxidation of the 5-*exo*-hydroxylactone (**7**, X = H) may be due to a dipolar interaction with the lactone (Diagram I). In 0.02 M perchloric acid this compound is oxidised 12-times slower than the corresponding cyclic ether, itself oxidised 3-times slower than 2-*exo*-hydroxybicyclo-[2,2,1]heptane.[9] We found that the 3-*exo*-hydroxylactone (**5**, X = H), in which any dipolar interaction with the



(I)

lactone would clearly be at right angles, is oxidised only 3-times faster than the 5-*exo*-hydroxylactone (**7**, X = H), at a rate therefore still 12-times slower than 2-*exo*-hydroxybicyclo-[2,2,1]heptane. Moreover, comparison of the rates of the *exo*-bromo *exo*-hydroxy compounds (**5**, X = Br and **7**, X = Br) shows an even smaller difference, around twofold. The very slow rate of oxidation of **7** (X = H) remains therefore unexplained.

The 3-*endo*-hydroxylactone (**6**, X = H) is oxidised about 4-times faster than the 3-*exo*-hydroxylactone (**5**, X = H). This difference, like those previously reported,[3]

lends little support to the idea[10] of control by steric strain in the product.

The 3-oxo-lactone (**4**, X = H) is oxidised very slowly, as expected, probably because of difficulty anticipated in enolisation.[3] This 3-oxo-lactone does not readily form a stable hydrate in contrast to the 5-oxo-lactones in which hydrate formation occurs[3] unless hindered by a bulky 3-*endo*-group, and may account for the difficulties encountered[9,11] in the isolation of such lactones. Ketones which form hydrates are oxidised more readily.[3] Absence of observed hydrate formation at the 3-position in **4**(X = H) suggests that perhaps hydrate formation at the 5-position is influenced by an interaction with the lactone.

Ranganathan *et al.*[1] correct the structures assigned[12] to compounds formed by bromolactonization of the cyclopentadiene-citraconic anhydride adduct. We had also from NMR spectra realised[13] that the assignment was incorrect and confirmed the reassigned structure **8** for the adduct m.p. 160° by converting it to the dibromolactone (**9**) by procedures shown[14] to cause inversion of configuration at the 3-position. The two bromines in **9** are clearly seen to be di-*exo* from the lack of an AB quartet for the 7-position protons in the NMR spectrum.

The absence of the spectrum of a doublet (6-exo-H) δ 4.5–4.7, triplet (1 – H) δ3.2–3.4, doublet (2-*exo*-H) δ2.9–3.1, characteristic[3] of a 1-*exo*-proton, and the presence of a doublet (6-*exo*-H) δ4.98 and doublet of doublets (1–H) δ2.87, clearly shows that the Me group must be attached at the 2-*exo* position.

EXPERIMENTAL[15]

Kinetic determinations were made by methods reported[3] previously.

6 - endo - *Hydroxy* - 5 - exo - *iodo* - 3 - *methylene bicyclo*[2,2,1] *heptane* - 2 - endo - *carboxylic acid*, *γ-lactone* (**2**, X = I). 3-Methylenebicyclo[2,2,1]hept-5-ene-2-carboxylic acid (29.9 g) was added to sat $NaHCO_3$ aq (800 ml) with stirring. Iodine soln[5] (KI 100 g, I_2 50 g, H_2O 300 ml) (160 ml) was added dropwise over 3.5 hr. The mixture was stirred at r.t. for 20 min and then extracted with ether (3 × 400 ml). The combined ethereal soln was washed with dil$Na_2S_2O_3$ aq (50 ml) and water (2 × 100 ml), dried ($MgSO_4$), filtered and evaporated to give a white solid (26.0 g). Recrystallization from ether gave colourless crystals (24.7 g) (65.1% after recovery of *exo*-acid). m.p. 82–3°. (Found: C, 38.92; H, 3.21; I, 46.01. $C_9H_9IO_2$ requires; C, 39.15; H, 3.29; I, 45.94); IR: ν_{max} (KBr) 1970–1995 (strong), 1655 (weak); NMR: δ ($CDCl_3$): 5.30 (m, 3H, C = CH_2 and 6-*exo*-H), 3.98 (d, 1H, 5-*endo*-H), 3.36 (t, 1H, 1-H), 3.20 (broad singlet, 2H, 2-*exo*- and 4-H), 2.41 and 1.95 (AB quartet, J = 12 Hz, 2H, 8-H).

3-*Methylene bicyclo*[2,2,1]*hept-5-ene*-2-exo-*carboxylic acid* (**1**, CO_2H exo). The mother liquor of the ether extraction was acidified at 0° with conc HCl and extracted with ether (3 × 400 ml). The ethereal soln was washed with 1 M NaS_2O_3 (50 ml) and water (2 × 50 ml), dried ($MgSO_4$), filtered and evaporated to give pale yellow crystals (9.25 g) that were crystallized from petrol (b.p. 40–60°) to give colourless crystals m.p. 55–56°. (Found: C, 71.74; H, 6.72. $C_9H_{10}O_2$ requires: C, 71.98; H, 6.71%); IR: ν_{max} (KBr) 3300–2600 (broad), 1700 (CO), 1652 (C=C). NMR: δ($CDCl_3$), 9.60 (s, 1H, CO_2H), 6.22 (s, fine coupling, 2H, 5 + 6H), 5.15 (dd, 2H, C = CH_2), 3.25 (broad singlet, 2H, 1 + 4H), 2.85 (d, 1H, 2-*endo*-H), 1.92 and 1.63 (AB quartet. J = 10 HZ, 2H, 7-*syn*-H and 7-*anti*-H).

6 - endo - *Hydroxy* - 3 - *methylenebicyclo*[2,2,1]*heptane* - 2 - endo-*carboxylic acid*, *γ-lactone* (**2**, X = H). The iodolactone (**2**, X = I, 7.00 g, 25.4 mmole) was placed in a flask and tri-n-butyl tin hydride (8.63 g, 30 mmole) added. A trace of 2,2'-azobis-(2-methylproprionitrile) and anhydrous ether (25 ml) were added, and the apparatus flushed with N_2. It was then irradiated with UV light (264 nm) for 10 min and set aside for 48 hr. The solvent was then removed by evaporation and the residue chromatographed on silica gel (100 g), eluting with $CHCl_3$ to give a colourless mobile liquid (4.56 g). Crystallization from petrol (b.p. 40–60°) (115 ml) at 4° gave a white solid (3.00 g, 79%). m.p. 30–31°. (Found: C, 71.97; H, 6.60. $C_9H_{10}O_2$ requires: C, 71.98; H, 6.71%); IR: ν_{max} (KBr) 1765 (strong, broad), 1660 (w); NMR: δ ($CDCl_3$) 5.14 (broad singlet, 2H, C=CH_2), 4.94 (t, 1H, 6-*exo*-H), 3.38 (t, 1H, 1-H), 3.03 (broad d, 1H, 2-*exo*-H), 2.91 (broad s, 1H, 4-H), 1.70 (m complex, 4H, 5-H and 7-H).

6-endo-*Hydroxy*-3-*oxobicyclo*[2,2,1]*heptane*-2-endo-*carboxylic acid*, *γ-lactone* (**4**, X = H). The methylene-lactone (**2**, X = H, 3.0 g, 0.02 mole) was dissolved in dichloromethane (50 ml). Ruthenium dioxide dihydrate (5 mg) was added and the mixture stirred vigorously. Sodium metaperiodate (8.52 g, 0.04 mole) in water (100 ml) was added over 20 min and the mixture was stirred for 5 hr and then allowed to stand overnight. Iso-propyl alcohol (2 ml) was then added and the organic layer separated. The aqueous phase was extracted with dichloromethane (3 × 50 ml). The combined ogranic layers were dried ($MgSO_4$), filtered through celite and evaporated to dryness to give a dark brown solid. This was crystallised, using charcoal, from benzene to give a white solid which was recrystallized from benzene (10 ml)/ether (40 ml) to give white crystals (2.24 g, 74%), m.p. 186–7°, lit[4], 157–60°. (Found: C, 63.04; H, 5.27. Calc. for $C_8H_8O_3$: C, 63.15; H, 5.30%); IR., N.M.R. as described.[4]

3,6-Diendo-*dihydroxybicyclo*[2,2,1]*heptane*-2-endo-*carboxylic acid*, *γ-lactone* (**6**, X = H). The oxolactone (**4**, X = H; 2.14 g, 14 mmole), was dissolved in dry THF (50 ml), diborane soln (0.37 m; 20 ml) added and the soln stirred at room temp. for 3 hr and set aside for 16 hr. Tlc indicated some ketone still present. Diborane soln (5 ml) was added and stirred at room temp. for 4 hr and set aside for 48 hr. Ether (50 ml) and sat $NaHCO_3$ (50 ml) were added and the organic layer separated. The aqueous layer was extracted with ether (1 × 50 ml) and chloroform (4 × 50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to give a white crystalline solid (2.36 g) which was chromatographed on silica gel to give a white solid (1.69 g), crystallized from benzene to give a white solid (1.21 g, 55.8%). m.p. 199–201°. (Found: C, 62.12; H, 6.51. $C_8H_{10}O_3$ requires: C, 62.32; H, 6.54%); IR: ν_{max} (KBr) 3420 (med. broad), 1750 (s); NMR: δ($CDCl_3$) 4.91 (overlapping d of d, 1H, 6-*exo*-H), 4.53 (d of d, 1H, 3-*exo*-H,), 3.90 (broad singlet, exchangeable, OH), 3.26 (tri, 1H, 1-H), 2.73 (d of d, 1H, 2-*exo*-H), 2.50 (broad singlet, 1H, 4-H), 2.1–1.3 (multiplet, 4H, 7-H and 5-H).

5-exo-*Bromo*-3-exo-6-endo-*dihydroxybicyclo*[2,2,1]*heptane*-2-endo-*carboxylic acid*, *γ-lactone* (**5**, X = Br). Prepared as described[4] except that it was found advantageous to hydrolyse the intermediate cyclopentadiene-acetoxyacrylate adduct in aqueous ethanolic KOH at room temp. for 7–10 days. White solid m.p. 137–9° dec; lit.[4] 128–30°. (Found: C, 41.08; H, 3.87; Br, 34.34. $C_8H_{10}O_3$ requires: C, 41.22; H, 3.89; Br, 34.29%). IR, NMR spectra as described.[4]

3-exo-6-endo-*Dihydroxybicyclo*[2,2,1]*heptane*-2-endo-*carboxylic acid*, *γ-lactone* (**5**, X = H). Prepared as described[4] except that the product was purified by repeated crystallisation from ether to give a white solid m.p. 177–80° dec.; lit.[4] 123–5°. (Found: C, 61.92; H, 6.73. $C_8H_{10}O_3$ requires: C, 62.32; H, 6.54%); IR as described[4]; NMR (not previously described): δ($CDCl_3$). 4.72 (overlapping d of d, 1H, 6-*exo*-H), 4.05 (s, 1H, 3-*endo*-H), 3.32 (s, 1H, exch OH), 3.17 (tri, 1H, 1-H), 2.42 (d, 2H, 2 + 4-H), 2.17–1.23 (complex, 4H, 3- and 7-H). This compound gave on tlc on silica gel in 95:5 v/v $CHCl_3$–MeOH one spot, distinct and separable from the *endo*-hydroxy compound.

3 - exo - 5 - exo - *Dibromo* - 6 - endo - *hydroxy* - 2 - exo - *methylbicyclo*[2,2,1]*heptane* - 2 - endo - *carboxylic acid*. *γ-lactone* (**9**). 5 - exo - Bromo - 6 endo - hydroxy - 2 *exo* - methylbicyclo [2,2,1]heptane-2,3-endo-dicarboxylic acid, *γ-lactone* (5 g, 0.0182 mole) was suspended in dry CCl_4 (300 ml). Red mercuric oxide (3.2 g) and Br_2(3 g) in dry CCl_4 (50 ml) was added. The mixture was heated under reflux on a steam bath for 1.5 hr and then cooled and stirred with 8% $NaHCO_3$ (100 ml) for 0.25 hr. The organic layer was separated off and dried (Na_2SO_4), filtered and evaporated, and gave a white crystalline solid (8.17 g). Recrystallization from CCl_4 gave a white solid (5.63 g, 88.4%),

m.p. 132–136°. (Found: C, 34.78; H, 3.59. $C_9H_{10}Br_2O_2$ requires: C, 34.83; H, 3.23%); IR: ν_{max} (CCl_4) 1798 (s); NMR: δ ($CDCl_3$) 4.98 (d, J = 5 Hz, 1H, 6-*exo*-H), 4.24 (s, 1H, 5-*endo*-H), 3.90 (s, 1H, 3-*endo*-H), 3.01 (s, 1H, 4-H), 2.87 (dd, 1H, 1-H), 2.42 (s, 2H, 7-*syn*-H, 7-*anti*-H), 1.40 (s, 3H, C–CH_3).

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[15]M.ps are uncorrected. Unless otherwise stated. IR spectra were recorded on a Perkin Elmer model 377 and NMR spectra on a Varian EM360 instrument using TMS as internal standard. Silica gel G (Stahl) was used for thin layer chromatography. Elemental analyses were performed by Dr. Crouch, School of Pharmacy, University of London.