Preparation and Oxidation with Chromic Acid of All Six 3-Bromo-5-hydroxy- and -5-oxo-bicyclo[2.2.1]heptane-2,6-carbolactones

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The title compounds have been prepared and their rates of oxidation with chromic acid determined. *endo*-Hydroxy-(3) are oxidised faster than *exo*-hydroxy-compounds (1). Strain in the product is therefore unlikely to be a rate-determining factor. The 3-*exo*-bromo-ketone (2a) forms a stable hydrate (4) and is oxidised faster than the 3-*exo*-bromo-5-*exo*-alcohol (1a). The stable 3-*endo*-bromo-ketone (2b) is oxidised more slowly than the 3-*endo*-bromo-alcohols (1b) and (3b). Compounds with a 3-*endo*-bromo-substituent [(1b), (2b), and (3b)] showed analgetic activity.

THE *exo*-hydroxy-lactone (1c) is surprisingly difficult to oxidise;[1] it was suggested that this could be due to steric strain in the product (2c), an explanation similar to that later put forward[2] to account for observations on the oxidation of benzocyclobutenols. It has been suggested that this strain in the ketone may not be fully developed in the transition state, but neverthless there is a correlation between such strain and lowered rates.[3] In contrast Aswathy *et al.* proposed[4] that the resistance to oxidation was due to dipolar interaction. These authors[4] found that the oxo-lactone (2c) was oxidised slightly faster than the corresponding alcohol (1c), and briefly reported (in a footnote) that it appeared to be rapidly converted into a hemiacetal in methanol.

We now report the preparation and oxidation of some new bromo-hydroxy-lactones, including two *endo*-hydroxy-lactones. Previously described compounds have all been *exo*-hydroxy-lactones. The results are given in Table 1.

TABLE 1

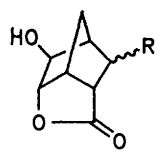
Rates of oxidation of hydroxybicyclo[2.2.1]heptanecarbolactones by 5×10^{-4}M-chromic acid in 4×10^{-2}M-perchloric acid at 31 °C

Compound	Rate (l mol^{-1} min^{-1})	k_{rel}
exo-OH, *exo*-Br (1a)	0.260	0.633
endo-OH, *exo*-Br (3a)	8.81	21.4
exo-OH, *endo*-Br (1b)	0.271	0.682
endo-OH, *endo*-Br (3b)	1.48	3.60
exo-OH (1c)	0.411	1.00
=O, *exo*-Br (2a)	3.56 †	8.66
=O, *endo*-Br (2b)	0.069	0.27

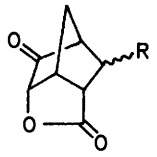
† The rate of oxidation of the hydrate (4) is similar.

The difference (over thirty-fold) in rates for compounds (1a) and (3a), which are oxidised to the same product (2a), does not support the idea[1] of steric strain in the product being the dominant factor. The five-fold difference in rates for compounds (1b) and (3b), which are both oxidised to the same product (2b), though less pronounced, is qualitatively similar to that of the first pair. This difference is similar to that between *exo*- and *endo*-norbornanols.[2] It has recently been suggested[5] that the rate of oxidation is reduced if the C–H bond to be broken is less accessible. From this point of view the *exo*-alcohols have the less accessible *endo* C–H bond and might therefore be oxidised more slowly.

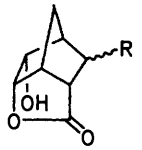
The six-fold difference in rates for the *endo*-hydroxy-compounds (3a and b) suggests some transannular



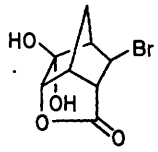
(1) a; R = *exo*–Br
b; R = *endo*–Br
c; R = H



(2) a; R = *exo*–Br
b; R = *endo*–Br
c; R = H
d; R = *exo*–CO_2H
e; R = *endo*–CO_2H
f; R = CO_2Me



(3) a; R = *exo*–Br
b; R = *endo*–Br



(4)

interaction. Steric hindrance to chromate ester formation (rate decreasing) and relief of steric strain in decomposition of chromate ester (rate increasing) have both been proposed, and one or other may be dominant in conditions of varying acidity.[6] Sterically hindered alcohols may be oxidised by a different mechanism.[3,7] ^{1}H N.m.r. spectra of the *endo*-bromo-compound (3b) show that the proton of the hydroxy-group is slow to be exchanged (Table 2 footnote §).† This could hinder chromate ester formation and so reduce the rate of oxidation in comparison with the corresponding *exo*-bromo-compound.

There is a startling difference in the stabilities of the oxo-lactones towards water. The *exo*-bromo-oxo-

† Details of ^{1}H n.m.r. spectra (Tables 2 and 3) and a discussion of their significance are deposited as Supplementary Publication No. SUP 21956 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin II*, 1975, Index issue.

[1] E. Crundwell and W. Templeton, *J. Chem. Soc.*, 1964, 1400.
[2] P. Muller, *Helv. Chim. Acta*, 1970, **55**, 1869; 1971, **54**, 2001.
[3] P. Muller and J. C. Perlberger, *J. Amer. Chem. Soc.*, 1975, **97**, 6862.
[4] A. K. Aswathy, J. Rocek, and R. M. Moriarty, *J. Amer. Chem. Soc.*, 1967, **89**, 5400.
[5] E. J. Corey and L. S. Melvin, *Tetrahedron Letters*, 1975, 929.
[6] J. Rocek, F. A. Westheimer, A. Eschenmoser, L. Moldovanyi, and J. Schreiber, *Helv. Chim. Acta*, 1962, **45**, 2554.
[7] H. Kwarte and J. H. Nickle, *J. Amer. Chem. Soc.*, 1973, **95**, 3394.

lactone (2a) is rapidly converted in moist air into the hydrate (4), which can be isolated. The ketone may be regenerated by sublimation. Hydrate formation in aqueous solution is well known [8] in aldehydes with electron-withdrawing substituents, and some stable hydrates can be isolated. Ketones are considerably less prone [8] to undergo hydration in aqueous solution, and stable hydrates cannot normally be isolated. Perhaps hydrate formation relieves steric strain in the ketones (2a and c).

In contrast the *endo*-bromo-oxo-lactone (2b) is stable. Perhaps hydrate formation is resisted by steric interaction with the *endo*-bromine atom. The *endo*-carboxy-oxo-lactone [9] (2e) is also stable. Preliminary work suggests that the corresponding *exo*-carboxy-oxo-lactone (2d) forms a hydrate, and that similar relationships apply to the *endo*- and *exo*-methoxycarbonyl-oxo-lactones (2f). Bulky substituents are known [8] to decrease the extent of hydrate formation in aldehydes.

There is a considerable difference (over thirty-fold) in rates of oxidation of the oxo-lactones. It has been proposed that the acid-catalysed oxidation of ketones by chromic acid proceeds *via* preliminary enolisation.[10] In bicycloheptanes enolisation could probably not occur *via* removal of the bridgehead [11] proton at position 4, and the great stability in acid of norbornane-2,6-carbolactones [12] makes enolisation *via* removal of the proton at position 6 also unlikely, as it would lead to considerable ring strain at that carbon atom. The rate for the *endo*-bromo-ketone (2b) is less than that for the corresponding *exo*-alcohol, indeed so small that it approaches that of decay of the reagent. In contrast, the *exo*-bromo-ketone (2a) is rapidly oxidised, perhaps because it is readily hydrated, so that chromate ester formation can proceed. Hydration is a significant factor in the oxidation of aldehydes by chromic acid,[13] in which the rate-limiting step is then cleavage of the C–H bond. The isolated hydrate (4) was oxidised at the same rate as its parent ketone.

Because of the depressant effects of butyrolactone on the central nervous system [14] the new compounds listed in Table 1 were tested for such activity. The three compounds with a 3-*endo*-bromo-substituent [(1b), (2b), and (3b)] all showed some analgetic activity in the mouse in the hot plate test, the most active (3b) having an ED_{50} of 60 mg kg^{-1} (codeine ED_{50} 17 mg kg^{-1}). The three compounds with a 3-*exo*-bromo-substituent [(1a), (2a), and (3a)] were all inactive.

EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 377 spectrophotometer. Elemental analyses were performed by Dr. Crouch, School of Pharmacy, University of London. All compounds showed only one spot on t.l.c. (silica gel; 95 : 5 v/v chloroform–methanol).

3-exo-*Bromo*-5-exo-*hydroxybicyclo*[2.2.1]*heptane*-2-endo,6-endo-*carbolactone* (1a).—3-*exo*-Bromobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid [15] (6.42 g) was stirred in suspension in 90% formic acid (40 cm^3) at 45—50 °C. Hydrogen peroxide (30%; 50 cm^3) was added dropwise over 45 min. The mixture was stirred at 50 °C for 1 h and then slowly poured into saturated sodium hydrogen carbonate solution (300 cm^3). Solid sodium hydrogen carbonate was added until the solution was alkaline to litmus. It was then extracted with chloroform (4 × 100 cm^3), and the extract was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated. The residue was crystallised from benzene to give white *microcrystals*, m.p. 134—136° (5.10 g, 74%) (Found: C, 41.4; H, 3.9; Br, 34.35. $C_8H_9BrO_3$ requires C, 41.2; H, 3.9; Br, 34.3%), $\nu_{max.}$ (KBr) 3 420m and 1 765s cm^{-1}.

3-endo-*Bromo*-5-exo-*hydroxybicyclo*[2.2.1]*heptane*-2-endo,6-endo-*carbolactone* (1b).—This compound was similarly prepared from 3-*endo*-bromobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid [15] as a white *powder*, m.p. 155—156° (48%) (Found: C, 41.65; H, 3.85; Br, 34.3%), $\nu_{max.}$ (Nujol) 3 480m and 1 765s cm^{-1}.

3-endo-*Bromo*-5-*oxobicyclo*[2.2.1]*heptane*-2-endo,6-endo-*carbolactone* (2b).—The alcohol (1b) (5.7 g) was dissolved in acetone (180 cm^3) and water (90 cm^3). Ruthenium dioxide dihydrate (from ruthenium chloride) (300 mg) was added and the mixture stirred at room temperature. Sodium periodate (8.55 g) was added over 5 h and the mixture set aside for 16 h. Isopropyl alcohol (20 cm^3) was then added and the mixture filtered through Celite; the filtrate was extracted with ethyl acetate (2 × 250 cm^3) and the extract was dried ($MgSO_4$) and evaporated. The residue crystallised from acetone–petroleum (b.p. 60—80 °C) as white *microcrystals*, m.p. 184—185° (4.38 g, 77.5%) (Found: C, 41.6; H, 2.95; Br, 34.5. $C_8H_7BrO_3$ requires C, 41.55; H, 3.05; Br, 34.65%), $\nu_{max.}$ (Nujol) 1 785s and 1 775s cm^{-1}.

3-exo-*Bromo*-5,5-*dihydroxybicyclo*[2.2.1]*heptane*-2-endo,6-endo-*carbolactone* (4).—The alcohol (1a) was similarly oxidised to give, on evaporation of the extract, a white solid which crystallised from acetone–petroleum (b.p. 60—80 °C) as a white *powder*, m.p. 124—125° (73%) (Found: C, 38.65; H, 3.55; Br, 32.0. $C_8H_9BrO_4$ requires C, 38.55; H, 3.6; Br, 32.15%), $\nu_{max.}$ (KBr) 3 320m and 1 768s cm^{-1}.

3-exo-*Bromo*-5-*oxobicyclo*[2.2.1]*heptane*-2-endo,6-endo-*carbolactone* (2a).—The above crude hydrate (4) was sublimed at 110 °C and 80 N m^{-2} to give a white *solid*, m.p. 126—128° [53% from the alcohol (1a)] (Found: C, 41.65; H, 3.0; Br, 34.65%), $\nu_{max.}$ (KBr) 1 810s and 1 765 cm^{-1}. This compound is slowly converted into the hydrate (4) in moist air.

3-exo-*Bromo*-5-endo-*hydroxybicyclo*[2.2.1]*heptane*-2-endo,-6-endo-*carbolactone* (3a).—The ketone (2a) (316 mg) was dissolved in dry tetrahydrofuran (20 cm^3) under dry nitrogen. The solution was stirred in an ice-bath and 0.685M-diborane (2 cm^3) in tetrahydrofuran was added. After 1 h the mixture was allowed to reach room temperature and then stirred for 20 h. Diethyl ether (20 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3) were then added. The ethereal layer was separated and the aqueous layer was extracted with diethyl ether (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to

[8] For a review see R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4**, 1.
[9] K. Alder, H-H. Molls, and R. Reeber, *Annalen*, 1958, **611**, 7.
[10] J. Rocek and A. Riehl, *J. Amer. Chem. Soc.*, 1967, **89**, 6691.
[11] For a review see G. L. Buchanan, *Chem. Soc. Rev.*, 1974, 41.
[12] D. R. Storm and D. E. Koshland, *J. Amer. Chem. Soc.*, 1972, **94**, 5805.
[13] For a review see T. Rocek in ' The Chemistry of the Carbonyl Group,' ed. S. Patai, New York, 1966, p. 461.
[14] R. H. Roth and Y. Suhr, *Biochem. Pharmacol.*, 1970, **19**, 3001, 3013.
[15] K. Alder, F. Brochhagen, C. Kaiser, and W. Roth, *Annalen*, 1955, **593**, 1.

give a viscous oil, which was chromatographed on silica gel in chloroform to give a white *solid*, m.p. 132—133° (210 mg, 66%) (Found: C, 4.25; H, 3.8; Br, 34.5%), $\nu_{max.}$ (KBr) 3 380m and 1 752s cm^{-1}.

3-endo-*Bromo*-5-endo-*hydroxybicyclo*[2.2.1]*heptane*-2-endo,6-endo-*carbolactone* (3b).—The ketone (2b) was similarly treated to give a white crystalline *solid*, m.p. 192—194° (decomp.) (65%) (Found: C, 41.4; H, 4.0; Br, 34.45%), $\nu_{max.}$ (KBr) 3 360m, 1 786s, and 1 772s cm^{-1}.

The 5-*endo*-hydroxy-compounds (3a and b) were also prepared from the ketones by reduction with zinc borohydride in dry diethyl ether. The stable ketone (2b) also gave the alcohol (3b) on reduction with sodium borohydride in ethanol.

Kinetic Determinations.—These were made by methods similar to those reported previously.[4] Separate solutions in 9 : 1 acetic acid–water of chromic acid (1×10^{-3}M) and of the substrate (2×10^{-2}M) plus perchloric acid (4×10^{-2}M) were kept at 31 ± 0.1 °C for at least 15 min. Equal volumes were then mixed and the absorption at 350 nm was measured with a Gilford 240 spectrophotometer at 31 ± 0.1 °C. A similar determination without the test substance was carried out concurrently. The readings were corrected for reagent decay and plotted as log absorption against time to obtain first-order rate constants, which were converted into second-order rate constants by considering the initial reactant concentration. The results in Table 1 are the means of three determinations with variation less than ±5%. Good straight lines were obtained for all the alcohols. The ketones gave initial straight lines but the rate slowly decreased. Results in Table 1 are for the initial straight lines.

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