Mechanism of C(8)-Bromination of 3,3-Dibromocamphor

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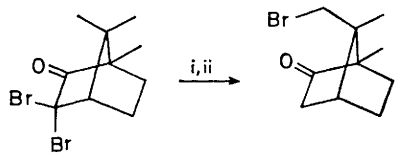
Investigation of the mechanism of C(8)-bromination of 3,3-dibromocamphor using deuterium-labelled precursors indicates that the process may involve 2,3-*endo*-methyl shifts.

In previous papers[1] we suggested that the bromination of 3,3-dibromocamphor (**1**) could involve a 2,3-*endo*-methyl shift† and that direct C(8)-bromination of the camphor system would occur. The practical result of this proposal was a short, simple synthesis of optically active 8-bromocamphor (**2**),‡ a potentially useful intermediate in terpenoid synthesis.[5] However, the successful outcome of these investigations could not be considered as direct evidence for the occurrence of a 2,3-*endo*-methyl shift during the bromination process since alternative explanations for the observed regiospecificity are possible.

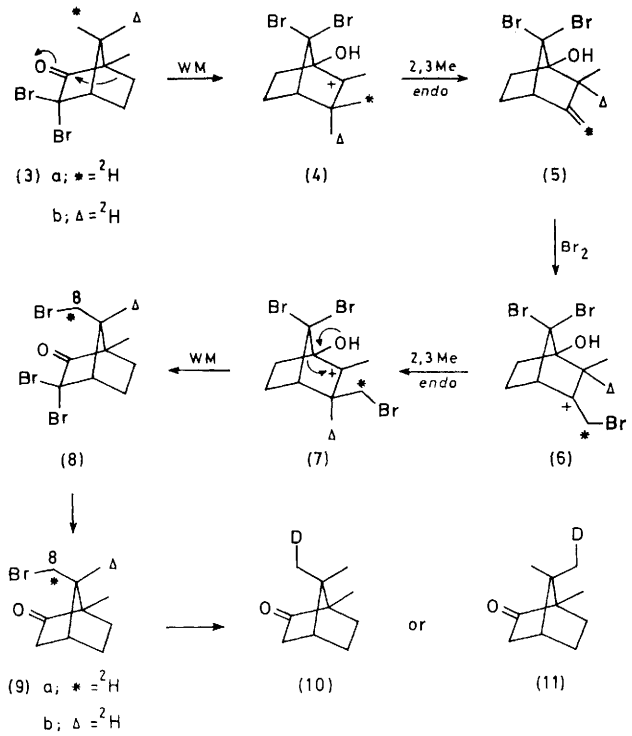


(1) (2)

i, Br_2–$ClSO_3H$; ii, Zn–HBr or Zn–HOAc.

† 2,3-*endo*-Hydride (refs. 2, 3) and 2,3-*endo*-methyl shifts (ref. 3) have previously been reported in bornane and norbornane systems, respectively.

‡ The n.m.r. signals for the C(8)-hydrogens of 8-bromocamphor (**2**), recorded on a 100 MHz spectrometer, were previously reported (refs. 1, 4) as coincident singlets at 6·87 τ. Using a 220 or 270 MHz instrument, the expected AB quartet for the C(8)-methylene group is observed: H_A δ 3·10, H_B δ 3·15, J_{AB} 10·5 Hz. We have also observed a similar resolution of the C(8)-hydrogens in 8-benzoyloxycamphor when the n.m.r. spectrum is recorded on a 270 MHz instrument.



Scheme 1. *endo, endo* mechanism; *or Δ = ^{2}H; WM = Wagner–Meerwein rearrangement; 2,3-Me = Nametkin shift.

To elucidate the mechanism of C(8)-bromination of 3,3-dibromocamphor (**1**) we decided to perform this transformation using 8- and 9-deuteriated starting material. Thus if the bromination mechanism involves two *endo*-methyl shifts (Scheme 1; *endo, endo* mechanism) [8-^{2}H]-3,3-dibromocamphor (**3a**) should eventually provide [8-^{2}H]-8-bromocamphor (**9a**). Subsequent hydrogenolysis would then yield [8-^{2}H]-camphor (**10**). Similarly, if [9-^{2}H]-3,3-dibromocamphor (**3b**) is used as starting material the final hydrogenolysis should provide [9-^{2}H]camphor (**11**) (*cf.* Scheme 1). An alternative analysis based on an *exo, endo* mechanism (*exo*-methyl shift followed by *endo*-methyl shift) would result in the conversion of [8-^{2}H]-3,3-dibromocamphor (**3a**) into [10-^{2}H]camphor, while 9-deuteriated material would provide [8-^{2}H]camphor (**10**).

[9-^{2}H]Camphor (**11**),[4] synthesized from (+)-9-bromocamphor ethylene acetal by reduction ($NaBD_4$–dimethyl sulphoxide)[6] and hydrolysis (6N HCl, Me_2CO) or from (+)-9-bromocamphor by reduction with tri-n-butyltin deuteride,[7,8] was converted into [9-^{2}H]-3,3-dibromocamphor (**3b**)[9] by sequential bromination with Br_2–HOAc[7] and Br_2.[1] Subsequent treatment of this compound with Br_2–$ClSO_3H$ followed by regioselective C(3)-debromination with Zn–HOAc or Zn–HBr[7] provided a mixture from which [*x*-^{2}H]-8-bromocamphor was isolated by column chromatography. The ^{1}H n.m.r. spectrum [δ(CCl_4, 270 MHz) 0·90 (3H, s), 1·13 (2H, t), 3·08, and 3·14 (2H, AB quartet, J_{AB} 11·0 Hz)] indicated that the deuterium label was located exclusively in the C(9)-methyl group and this was confirmed when hydrogenolysis with tri-n-butyltin hydride[7,8] provided [9-^{2}H]camphor (**11**) [δ(^{1}H, CCl_4, 270 MHz) 0·83 (2H, s), 0·87 (3H, s), and 0·94 (2H, t, *J* 2 Hz); δ (^{13}C, $CDCl_3$, 20 MHz) 9·3, 18·9 (t, *J* 19 Hz), and 19·8 p.p.m.].

In a similar fashion [8-^{2}H]camphor (**10**), synthesized from 8-bromocamphor (**2**) by reduction with tri-n-butyltin deuteride, was converted *via* the bromination–debromination sequence into [*x*-^{2}H]-8-bromocamphor. In this case the ^{1}H n.m.r. spectrum [δ(CCl_4, 270 MHz) 0·90 (3H, s), 1·14 (3H, s), and 3·12 (1H, m)] of the crude product indicated that the deuterium atom was located at the C(8)-position. Benzoylation ($PhCO_2K$–hexamethylphosphoramide) of the crude product followed by hydrolysis and column chromatography provided pure [8-^{2}H]-8-hydroxycamphor, which was subsequently converted into [8-^{2}H]-8-bromocamphor by treatment with PBr_3 in bromobenzene–quinoline.[4,10] Conversion of this product into [8-^{2}H]-8-iodocamphor[1a,5] followed by hydrogenolysis (H_2/Pd)[11] provided [8-^{2}H]camphor (**10**) [δ (^{1}H, $CDCl_3$, 270 MHz) 0·82 (2H, t, *J* 2 Hz), 0·91 (3H, s), and 0·96 (2H, s); δ (^{13}C, $CDCl_3$, 20 MHz) 9·2, 19·1, and 19·4 p.p.m. (t, *J* 19 Hz)]. The presence of a sharp singlet at δ 0·84 indicated that there was some undeuteriated camphor in this product and the loss of deuterium [from the C(8)-position] can be explained if intermediate (**5**) is involved in the bromination process. The alternative explanation involving the operation of an *exo, endo* mechanism is not consistent with the fact that the C(10)-methyl signal shows no evidence of deuteriation.

The experimental results described above are consistent with the proposed[1] occurrence of 2,3-*endo*-methyl shifts during the C(8)-bromination of 3,3-dibromocamphor (**1**) (Scheme 1).

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