A New Regiospecific Synthesis of 8-Bromocamphor [1]

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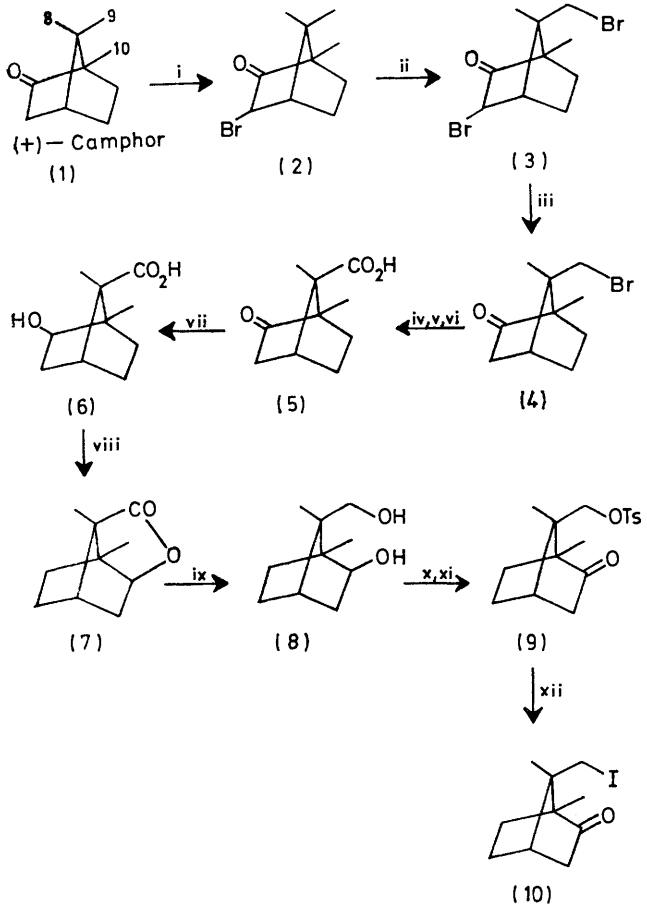
Bromination of 3,3-dibromocamphor(3,3-dibromobornan-2-one) followed by selective debromination provides a new regiospecific route to 8-bromocamphor (8-bromobornan-2-one).

THE direct bromination or sulphonation of (+)-camphor (1) and (+)-3-bromocamphor (2) at the C-8, C-9, and C-10 methyl groups has been the subject of considerable investigation since the end of the 19th century. Early literature and reviews [2] contain some misleading reports but recent re-appraisals [3] have considerably clarified the situation. As a result it may be concluded that bromination of (+)-camphor (1) in chlorosulphonic acid solution provides *partially racemic* 9-bromocamphor [3b] as the major product while the same conditions convert (+)-3-bromocamphor (2) into (+)-3,9-dibromocamphor (3). In the latter case selective debromination with Zn–HBr can be accomplished to provide a convenient route to (+)-9-bromocamphor (4).[3a,b] The well-known sulphonation of camphor with sulphuric or chlorosulphonic acid proceeds similarly with (+)-camphor (1) providing (±)-camphor-9-sulphonic acid and (+)-3-bromocamphor (2) providing (+)-3-bromocamphor-9-sulphonic acid.[3c,d] It is also evident that, in spite of early claims, bromination and sulphonation of camphor (1) do not result in functionalisation of C-8.[3]



SCHEME 1 Reagents: i, Br_2; ii, Br_2–$ClSO_3H$; iii, Zn–HBr; iv, KOAc–HOAc; v, HO^-–EtOH; vi, CrO_3–$MnSO_4$–H^+; vii, $NaBH_4$; viii, $CF_3{\cdot}CO_2H$–H_2SO_4; ix, $LiAlH_4$; x, TsCl–C_5H_5N; xi, CrO_3–C_5H_5N; xii, NaI–Me_2SO

The importance of 8-substituted camphor derivatives in mechanistic,[3b-d,4] spectroscopic,[5] and synthetic [3a,b] studies has prompted the development of several indirect methods of constructing these compounds. Synthetic routes [3c,4a] to 8-bromo- and 8-iodo-camphor have been developed but these involve eleven and nine step sequences and provide racemic mixtures. The only method previously available for the synthesis of optically active 8-bromo- or 8-iodo-camphor involves a twelve step stereospecific sequence (Scheme 1) starting from camphor.[3a,b,d] This route [3b,6a] is based on a key transformation involving the conversion of 2-oxobornan-9-oic acid (5) into the lactone (7) and was used by us in our recent synthesis of (−)-campherenone and related compounds.[6a] The method is tedious, however, and the overall yield of (−)-8-iodocamphor (10) from (+)-camphor (1) is ~6%; for this reason many attempts [7] have been made to provide a shorter and more efficient route to 8-substituted camphor derivatives, but these have failed. In general these unsuccessful efforts have tried to take advantage of the nearness of C-8 and the 2-hydroxy-group in isoborneol (11) to induce oxidation at the former position.

We have recently devised a solution to this problem by considering the mechanistic rationalisation which can be made to explain 9-bromination (and the absence

[1] Preliminary communication, C. R. Eck, R. W. Mills, and T. Money, *J.C.S. Chem. Comm.*, 1973, 911.

[2] (*a*) J. L. Simonsen and L. N. Owen, 'The Terpenes,' vol. II, 2nd edn., Cambridge University Press, London, 1957, pp. 395—427; (*b*) 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, Elsevier, Amsterdam, 1969, vol. IIc, pp. 207—215.

[3] (*a*) E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, 1959, **81**, 6305; (*b*) W. L. Meyer, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, 1967, **32**, 1754; (*c*) A. M. T. Finch, jun., and W. R. Vaughan, *J. Amer. Chem. Soc.*, 1969, **91**, 1416; (*d*) G. C. Joshi and E. W. Warnhoff, *J. Org. Chem.*, 1972, **37**, 2383.

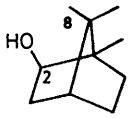
[4] (*a*) O. R. Rodig and R. J. Sysko, *J. Amer. Chem. Soc.*, 1972, **94**, 6475, and references therein; (*b*) *cf.* C. J. Collins and C. K. Johnson, *ibid.*, 1973, **95**, 4766.

[5] J. Hudec, personal communication; *cf.* M. T. Hughes and J. Hudec, *Chem. Comm.*, 1971, 805.

[6] (*a*) G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, *J.C.S. Chem. Comm.*, 1973, 235; (*b*) *cf.* G. L. Hodgson, D. F. MacSweeney, and T. Money, *J.C.S. Perkin I*, 1973, 2113.

[7] (*a*) W. Carruthers, 'Some Modern Methods of Organic Synthesis,' Cambridge University Press, Cambridge, 1971, pp. 184—185; (*b*) E. C. Woodbury, 'Intramolecular Functionalisations in the Camphane System,' Ph.D. Thesis, Harvard University, 1967, pp. 11—15; (*c*) E. R. Sigurdson, B.Sc. Thesis, University of British Columbia, Vancouver, 1973.

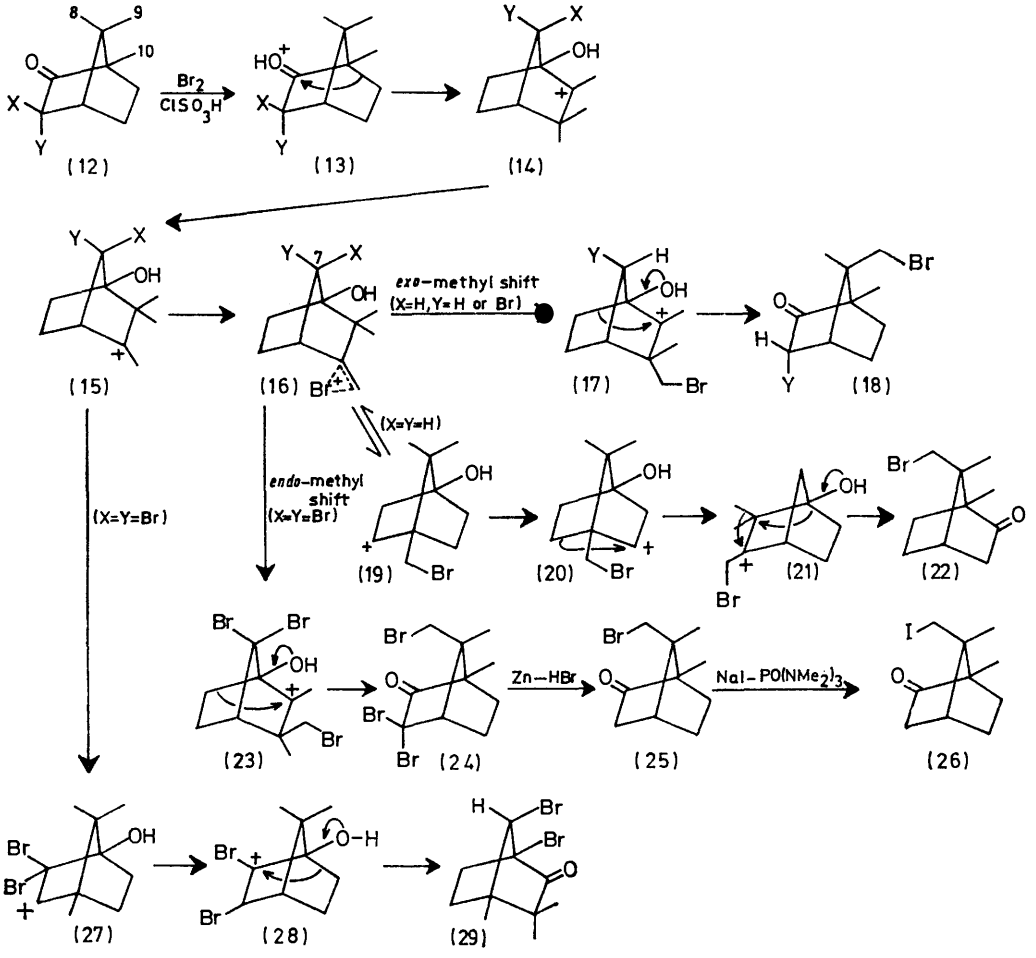
of 8-bromination) when camphor is treated with bromine and chlorosulphonic acid. Thus it has been assumed



(11)

that 9-bromination of (+)-camphor (12; X = Y = H) or (+)-3-bromocamphor (12; X = H, Y = Br) occurs by a sequence involving the bicyclic carbonium ion (15; X = H, Y = H or Br) (Scheme 2) or its alkene equivalent. Subsequent bromination accompanied by a 2,3-*exo*-methyl shift provides (17) which can rearrange to (+)-9-bromocamphor (18; Y = H) or (+)-3,9-dibromocamphor (18; Y = Br). It should be noted, however, that when (+)-camphor (12; X = Y = H) is brominated under these conditions the product is partially racemic 9-bromocamphor,[3b] *i.e.* (18; Y = H) + (22). The formation of (−)-9-bromocamphor (22) can be explained by Wagner–Meerwein rearrangement occurring during the bromination process [(15) ⟶ (16) ⟶ (19)] followed by the sequence of steps outlined in Scheme 2.

On the basis of these mechanistic considerations we presumed that direct 8-bromination could only occur if an unprecedented 2,3-*endo*-methyl migration accompanied the introduction of bromine. To promote such a rearrangement we considered the possibility of reversing the normal preference[8] for *exo*- over *endo*-methyl migration in bicyclo[2.2.1]heptyl compounds by having a bulky group in the 7-*syn*-position of the intermediate (16). This required the use of a 3-*exo*-substituted camphor derivative as starting material and since the substituent had to be capable of subsequent removal we synthesised 3,3-dibromocamphor (12; X = Y = Br)[9] from commercially available (+)-3-bromocamphor (12; X = H, Y = Br) in 95% yield and



SCHEME 2

[8] (*a*) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, 1967, **89**, 2590; (*b*) C. W. David, B. W. Everling, R. J. Kilian, J. B. Stothers, and W. R. Vaughan, *ibid.*, 1973, **95**, 1264 and references therein; *cf.* C. J. Collins and M. H. Lietzke, *ibid.*, 1973, **95**, 6841; (*c*) P. von R. Schleyer, *ibid.*, 1967, **89**, 699, 701; (*d*) H. C. Brown, *Chem. in Britain*, 1966, 199.

[9] This compound can also be prepared directly from camphor: *cf.* B. Shive, W. W. Crouch, and H. L. Lochte, *J. Amer. Chem. Soc.*, 1941, **63**, 2979; L. T. Scott and W. D. Cotton, *ibid.*, 1973, **95**, 2708.

subjected it to the conditions (Br_2–$ClSO_3H$) normally used to brominate camphor at C-9. The crude reaction product * was treated with zinc and hydrobromic acid and provided (+)-8-bromocamphor (25) in 75% overall yield. Although the physical properties of our (+)-8-bromocamphor differ from those previously reported they are in complete agreement (except for sign of rotation) with values obtained by Meyer and his co-workers.† Moreover our structural assignment was supported by conversion of (25) into (+)-8-iodocamphor (26), the enantiomer of which we had obtained previously [6a] by the sequence outlined in Scheme 1. Final confirmation of the structure of our product was obtained by *X*-ray crystallographic analysis [10] and by hydrogenolysis [$NaBH_4$–$(CH_3)_2SO$] and hydrolysis of the corresponding ethylene acetal to (+)-camphor (12; X = Y = H). A characteristic feature of the n.m.r. spectrum of 8-bromo- and 8-iodo-camphor is the presence of singlets at τ 6·87 and 7·02 (C-8 methylene protons) respectively, and we have used this as a test for the presence of these compounds. By contrast, the C-9 methylene protons in 9-bromocamphor appear as part of an ABX system at τ 6·76 and 6·41.

A by-product (*ca.* 10%) in the bromination–debromination sequence described above has been identified as 1,7-dibromo-3,3,4-trimethylnorbornan-2-one (29) on the basis of *X*-ray crystallographic analysis.[10] The formation of this compound can be explained by invoking Wagner–Meerwein rearrangement of the intermediate (15) *without* concomitant bromination. A subsequent 2,3-bromine shift followed by skeletal rearrangement could then provide the product (see Scheme 2).

A solution to the long-standing problem of direct 8-substitution of camphor has therefore been found and the implication of this result in terms of our general synthetic route to sesquiterpenes is described in a recent report.[11] The mechanism of our 8-halogenation reaction is unknown: as an alternative to the unusual *endo*-methyl migration considered above one could envisage a rearrangement mechanism ‡ involving 2,6-hydride shifts and more favourable 2,3-*exo*-methyl shifts.[8] It is hoped that work in hand will enable us to resolve this question.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. G.l.c. was carried out on a Varian Aerograph 90-P instrument with carrier gas (helium) flow-rate of 60 ml min^{-1} for 1/4 in columns and 170 ml min^{-1} for 3/8 in columns. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Routine i.r. spectra were recorded on a Perkin-Elmer Infracord 137 spectrophotometer and comparison spectra on a Perkin-Elmer 21 or 457 spectrophotometer. The 60 MHz n.m.r. spectra were recorded on a Varian A-60 or T-60 instrument and 100 MHz spectra on a Varian HA-100 or XL-100 instrument (tetramethylsilane as internal reference). Mass spectra were recorded on an A.E.I. MS9 spectrometer. Microanalyses were performed by Mr. P. Borda.

(+)-3,3-*Dibromocamphor* (12; X = Y = Br).—(+)-3-Bromocamphor (12; X = H, Y = Br) (55 g) and bromine (18 ml) were heated at 50 °C for 24 h in the dark, and the cooled reaction mixture was diluted with ether (200 ml) and water (200 ml). The excess of bromine was removed by addition of sodium metabisulphite and the aqueous layer was extracted with further portions (2 × 50 ml) of ether. Removal of the solvent and crystallization of the residue from light petroleum (b.p. 40—60°) afforded (+)-3,3-dibromocamphor (12; X = Y = Br) (73 g, 98%), m.p. 60 °C (lit.,[2,9] 61 °C), $[\alpha]_D^{25}$ +37·1° (*c* 1·67, 95% EtOH); $\nu_{max.}$ (CCl_4) 1765 cm^{-1}; τ (CCl_4) 9·08 (3H, s), 8·96 (3H, s), 8·80 (3H, s), and 7·26 (1H, m).

(+)-8-*Bromocamphor* [(+)-8-*Bromobornan*-2-*one*] (25).—(+)-3,3-Dibromocamphor (12; X = Y = Br) (73 g) was added to a cooled solution of chlorosulphonic acid (125 ml) and bromine (17·5 ml). The mixture was stirred at room temperature for 4 h and then carefully added dropwise to ice–water (*ca.* 200 g). The excess of bromine was destroyed with sodium metabisulphite and the aqueous solution extracted with ether. Work-up in the usual way provided a dark brown oil (92·5 g) which was dissolved in methylene chloride (400 ml). Zinc dust (134 g) was added to the solution and the stirred mixture treated with HBr gas for 4 h at 50 °C. After filtration, the solution was washed with water, saturated sodium hydrogen carbonate, and brine. Removal of the dried solvent provided a pale brown oil (54 g) which by g.l.c. examination (3% SE 30; 170 °C) was shown to consist of *ca.* 70—90% (+)-8-bromocamphor (25). Chromatography over alumina (grade IV, neutral or basic, 10 : 1) and elution with petroleum provided 8-bromocamphor as a pale yellow oil (70—80% yield). Sublimation followed by crystallization from light petroleum (b.p. 40—60 °C) gave (+)-8-*bromocamphor*, m.p. 83—85 °C; $[\alpha]_D^{25}$ +73·1° (*c* 1·17, 95% EtOH); $[\alpha]_D^{25}$ +76·7° (*c* 1·24, $CHCl_3$); $\nu_{max.}$ (CCl_4) 1740 cm^{-1}; τ (CCl_4) 9·09 (3H, s), 8·85 (3H, s), and 6·87 (2H, s); *m/e* 232/230 (M^+) and 151 (M − 80) (Found: C, 52·05; H, 6·5; Br, 34·8. $C_{10}H_{15}BrO$ requires C, 51·9; H, 6·5; Br, 34·6%).

The structure of (+)-8-bromocamphor (25) was confirmed by *X*-ray crystallographic analysis.[10]

A second component of the total reaction product was obtained by elution of the column with light petroleum–ether (9 : 1). Recrystallization of the product from this solvent pair provided (−)-1,7-*dibromo*-3,3,4-*trimethylnorbornan*-2-*one* (29), m.p. 123—124 °C, $[\alpha]_D^{23}$ −51·5° (*c* 1·57, $CHCl_3$); $\nu_{max.}$ (CCl_4) 1750, 1370, and 1355 cm^{-1}; τ (CCl_4) 9·00 (3H, s), 8·83 (3H, s), 8·70 (3H, s), and 5·90 (1H, s); *m/e* 312/310/308 (M^+), 231/229 (M − 79, M − 81), and 168/166 (M − 142, M − 144) (Found: C, 38·55; H, 4·4; Br, 51·7. $C_{10}H_{14}Br_2O$ requires C, 38·7; H, 4·5; Br, 51·5%). The structure of this compound was confirmed by *X*-ray crystallographic analysis.[10]

* *Added in proof:* Recent studies have shown that 3,3,8-tribromocamphor (24) can be isolated from this mixture and converted into (+)-8-bromocamphor (25) (P. Cachia, unpublished results).

† We thank Professor W. Meyer (University of Arkansas) for providing the spectral data and physical constants of a sample of (−)-8-bromocamphor prepared by the twelve step sequence previously used for the synthesis of optically active 8-substituted camphor derivatives (*cf.* Scheme 1).

‡ Recent studies in our laboratory have prompted us to consider that 8-bromination could also occur by an intramolecular bromination process.

[10] C. A. Bear and J. Trotter, *Acta Cryst.*, submitted for publication.

[11] C. R. Eck, G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, *J.C.S. Perkin I*, 1974, 1938.

(+)-8-*Iodocamphor* [(+)-8-*Iodobornan-2-one*] (26).—(+)-8-Bromocamphor (25) (62·5 g, 0·27 mol) was treated with sodium iodide (262 g, 1·75 mol) in hexamethylphosphoramide (500 ml) at 100 °C under nitrogen for 4 days. After cooling and diluting with water the reaction mixture was extracted with ether (4 × 200 ml) and the extract washed with sodium metabisulphite solution. Removal of the dried solvent provided a crude oil (45 g) which was shown by g.l.c. (3% SE 30, 160 °C) to be a mixture containing *ca.* 95% (+)-8-iodocamphor (26). Treatment of the reaction mixture with ethylene glycol and toluene-*p*-sulphonic acid provided 8-iodocamphor ethylene acetal which was purified by distillation. Subsequent hydrolysis (HCl–acetone) followed by crystallization of the product from light petroleum provided (+)-8-iodocamphor (26), m.p. 38—40 °C, $[\alpha]_D^{23}$ +86° (*c* 1·1, $CHCl_3$); $\nu_{max.}$ 1740 and 1415 cm^{-1}; τ ($CDCl_3$) 9·05 (3H, s), 8·86 (3H, s), and 7·02 (2H, s).

Hydrogenolysis of (+)-8-*Bromocamphor Ethylene Acetal.*—To a solution of (+)-8-bromocamphor ethylene acetal [11] (400 mg) in dimethyl sulphoxide (7 ml) was added an excess of sodium borohydride and the mixture stirred at 85 °C for 1 h. Water was added and the solution extracted with ether (4 × 80 ml). Removal of the solvent provided camphor ethylene acetal (250 mg) which was dissolved in acetone (10 ml) and treated with 6N-HCl (0·5 ml). After 24 h at room temperature most of the acetone was removed under reduced pressure and the solution extracted with ether. Removal of solvent from the washed and dried extract provided crude product (200 mg) which on sublimation at 60° and 0·5 mmHg gave (+)-camphor (12; X = Y = H) (46 mg), $[\alpha]_D^{25}$ +38·5° (*c* 4·54, $CHCl_3$). An authentic sample of (+)-camphor (Eastman Kodak Co.) gave $[\alpha]_D^{26}$ +41·7° (*c* 3·16, $CHCl_3$).

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