Further Observations on the Bromination of Camphor

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Recent investigations have shown that direct bromination of (+)-3,3-dibromocamphor provides a mixture of (+)-3,3,8-tribromocamphor, 1,7-dibromo-3,3,4-trimethylnorbornan-2-one, and 1,7-dibromo-4-dibromomethyl-3,3-dimethylnorbornan-2-one. Related studies have shown that (+)-3,9,9-tribromocamphor is a minor product in the known conversion of (+)-3-bromocamphor into (+)-3,9-dibromocamphor. The formation of these products can be rationalised by a general mechanistic scheme which also includes mechanisms for the conversion of (+)-camphor into partially racemic 9-bromocamphor, the acid-catalysed racemisation of camphor, and the isomerisation of (+)-3,9- to (−)-6,9-dibromocamphor.

THE mechanism proposed [1] for the direct bromination of camphor (1; X = Y = H) at C-9 involves formation of the intermediate (4; X = H, Y = Br) followed by the rearrangement sequence embodied in path C (Scheme). When camphor (1; X = Y = H) is used as starting material the product is partially racemic 9-bromocamphor [(8; X = Y = H) + (10)], and this observation [2] can be explained by invoking two reaction paths (A and C) for the postulated intermediate (4; X = Y = H) in the bromination process.† In contrast the operation of both these paths in the bromination of 3-bromocamphor (1; X = H, Y = Br) would be expected to provide 3,9-dibromocamphor (9; X = H, Y = Br) and its 6,9-isomer (8; X = H, Y = Br). The presence of the latter compound as a by-product in the synthesis of 3,9-dibromocamphor has not been established, but the reported [3a] conversion of 3,9-dibromocamphor (9; X = H, Y = Br) into 6,9-dibromocamphor (8; X = H, Y = Br) under strongly acidic conditions presumably involves formation of the intermediate (4; X = H, Y = Br) by reversal of path C followed by the sequence of rearrangements embodied in path A. In recent preparations of (+)-9-bromocamphor (10) from 3-bromocamphor (1; X = H, Y = Br) we have succeeded in isolating a minor product which we expected to be 6,9-dibromocamphor (8; X = H, Y = Br). However, the spectral characteristics of this compound led us to conclude that it was 3,9,9-tribromocamphor (13), and this assignment of structure and absolute configuration was confirmed by *X*-ray crystallographic analysis.[4] The formation of 3,9,9-tribromocamphor (13) can be explained by proposing that the intermediate (4; X = H, Y = Br) can undergo further bromination to a new intermediate (5; X = H, Y = Br), followed by a 2,3-*exo*-methyl shift and rearrangement to the camphor framework (path C).

In our previous report [1] we assumed that the crude product obtained from bromination of 3,3-dibromocamphor (1; X = Y = Br) was mainly 3,3,8-tribromocamphor (11). Recent investigations have shown that the major component of the crude product can be isolated and purified and that its spectral characteristics are indeed consistent with this structural assignment. In addition the purified product, when treated with Zn–HBr, can be converted in almost quantitative yield into

† The acid-catalysed racemisation [3b] of camphor (1; X = Y = H) involves the intermediate (3; X = Y = H) and the operation of a rearrangement sequence identical to that outlined in path A.

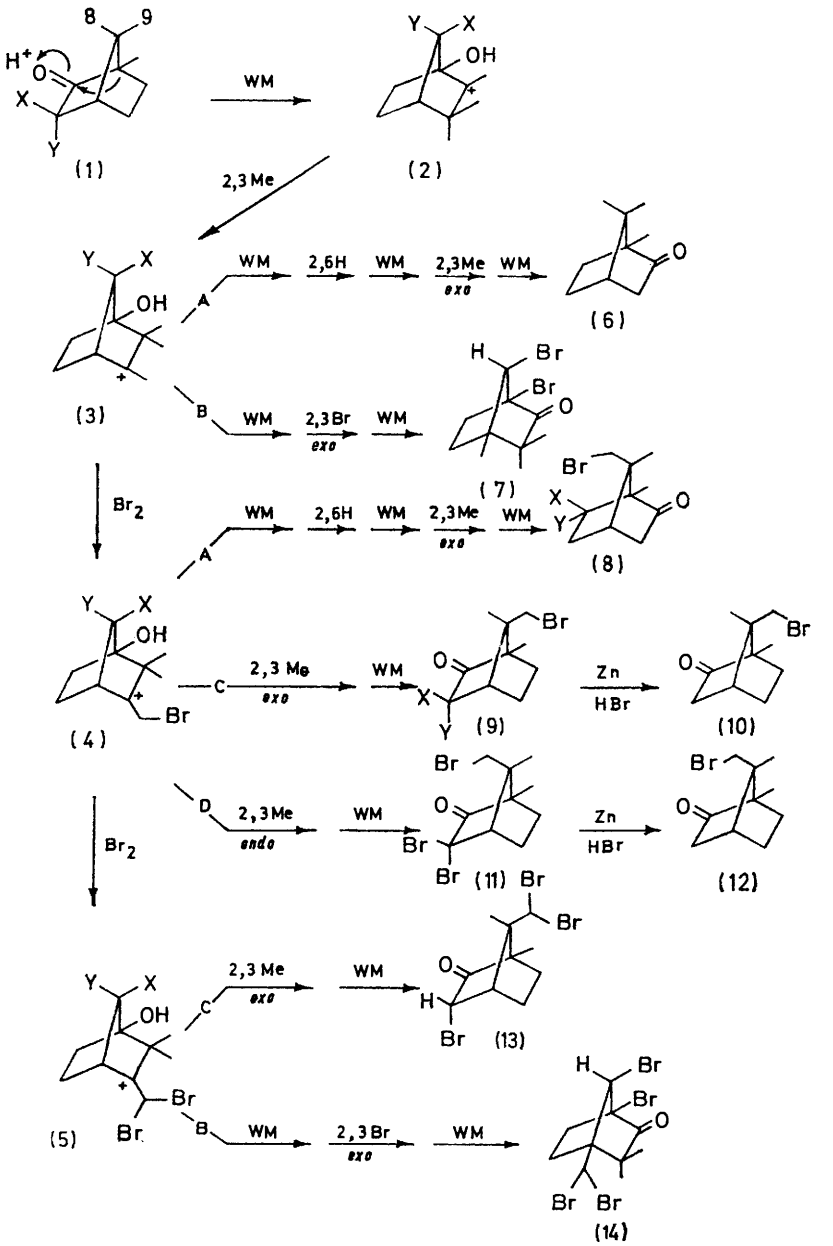
[1] C. R. Eck, R. W. Mills, and T. Money, *J.C.S. Chem. Comm.*, 1973, 911; *J.C.S. Perkin I*, 1975, 251.

[2] (*a*) W. L. Meyer, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, 1967, **32**, 1754; (*b*) H. Nishimitsu, M. Nishikawa, and H. Hagiwara, *Proc. Japan Acad.*, 1951, **27**, 285 (*Chem. Abs.*, 1952, **46**, 6112).

[3] (*a*) T. Miki, N. Nishikawa, and P. H. Hagiwara, *Proc. Japan Acad.*, 2955, **31**, 718; M. Nishikawa, *J. Pharm. Soc. Japan*, 1952, **72**, 634, 637, 640, 646 (*Chem. Abs.*, 1953, **47**, 6379, 6380); (*b*) *cf.* A. M. T. Finch, jun., and W. R. Vaughan, *J. Amer. Chem. Soc.*, 1969, **91**, 1416, and references cited therein.

[4] S. E. V. Phillips, D. Rendle, and J. Trotter, unpublished results.

8-bromocamphor (12). When 3,3-dibromocamphor (1; X = Y = Br) is treated with chlorosulphonic acid in the absence of bromine a remarkable transformation occurs and 3,3,8-tribromocamphor (11) is formed in *ca.* 50% yield. This reaction can be explained by assuming that 3,3-dibromocamphor (1; X = Y = Br) is acting as a brominating agent under these conditions. and is presumably formed *via* the intermediate (3; X = Y = Br) through reaction path B. In more recent investigations a second, minor product has been isolated and identified. On the basis of n.m.r. and mass spectral data the tetrabromo-structure (14) was assigned and this conclusion has been confirmed by *X*-ray crystallographic analysis.[4] The formation of (14) can be explained by

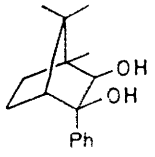


SCHEME WM = Wagner–Meerewein rearrangement; 2,6H = 2,6-hydride shift; 2,3Me = 2,3-methyl shift; 2,3Br = 2,3-bromine shift

Thus the transformation of (3; X = Y = Br) into (4; X = Y = Br) can occur and the subsequent operation of rearrangement sequence D provides 3,3,8-tribromocamphor (11). Two minor products are formed when 3,3-dibromocamphor is treated with bromine and chlorosulphonic acid. One of these, 1,7-dibromo-3,3,4-trimethylnorbornan-2-one (7), was reported previously [1] invoking the intermediate (5; X = Y = Br), which is subject to the rearrangement sequence embodied in path B. Thus in the bromination of 3,3-dibromocamphor (1; X = Y = Br), the formation of the products (7), (11), and (14) can be explained by postulating that intermediates (3), (4), and (5) (X = Y = Br) follow reaction paths B, D, and B, respectively.

The various reaction paths outlined in the Scheme explain the formation of the bromo-compounds obtained when camphor (1; X = Y = H), 3-bromocamphor (1; X = H, Y = Br), and 3,3-dibromocamphor (1; X = Y = Br) are treated with bromine and chlorosulphonic acid. Also included in the Scheme are mechanisms for the racemisation of camphor [3b] and the reported conversion of 3,9- to 6,9-dibromocamphor.[3a] The Scheme also implies that bromination of 3,3-dibromocamphor could provide 3,3,8,8-tetrabromocamphor by a 2,3-*endo*-methyl shift in the intermediate (5; X = Y = Br) followed by rearrangement to the camphor skeleton. However we have not been able to detect this compound in the crude product.

The predominance of 2,3-*exo*- over 2,3-*endo*-migrations in bicyclo[2.2.1]heptyl systems has been thoroughly documented by several groups.[3b,5-9] Although two authentic cases of 2,3-*endo*-hydride migration have been reported [10] there is an understandable reluctance to accept the possibility that 2,3-*endo*-methyl migration could occur. However we support the view that the preference for *exo*-proton exchange [11] and *endo*-bromination [2,12] in camphor as well as the preference for 2,3-*exo*-hydride,[13] hydroxy,[14] and methyl shifts [3,5-9] in norbornane derivatives are mainly due to steric effects.[9] The occurrence of 2,3-*endo*-hydride migrations in certain



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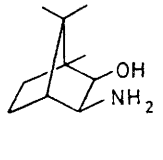

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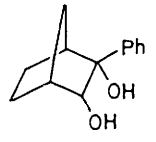

(17)

bornane derivatives [*e.g.* (15) and (16)] [10] and the reluctance of a norbornane derivative (17) to undergo a 2,3-*exo*-phenyl shift [15] may also be explained in this way.

EXPERIMENTAL

For general procedures see ref. 1.

(+)-3,3,8-*Tribromocamphor* (11).—*Method* (A). (+)-3,3-Dibromocamphor (1; X = Y = Br) (5 g) was added to cooled chlorosulphonic acid (25 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 acid was destroyed with sodium hydrogen carbonate and the aqueous solution was extracted with ether. Work-up in the usual way provided an orange oil (3.7 g) which was distilled (176° and 0.115 mmHg) to provide (+)-3,3,8-tribromocamphor (1.3 g, 53%). Chromatography over alumina (grade IV, neutral; 20 : 1) and elution with light petroleum (b.p. 30—60°) provided a product which, after sublimation and recrystallization from mixed hexanes, gave pure (+)-3,3,8-*tribromocamphor*, m.p. 35—41 °C; $[\alpha]_D^{25}$ +71.53° (*c* 0.720 in $CHCl_3$); $\nu_{max.}$ (CCl_4) 1 776 cm^{-1}; τ(CCl_4) 9.00 (3 H, s), 8.70 (3 H, s), 6.92 (1 H, d, *J* 4 Hz), and 6.74(d) and 6.25(d) (2 H, J_{AB} 12 Hz); *m/e* 392/390/388/386 (M^+), 311/309/307 (M − 79, M − 81), and 230/228 (311 − 81, 307 − 79) (Found: C, 31.25; H, 3.4; Br, 60.8. $C_{10}H_{13}Br_3O$ requires C, 30.8; H, 3.35; Br, 61.45%).

Method (B). (+)-3,3-Dibromocamphor (1; X = Y = Br) (17.3 g) was added to a cooled solution of bromine (4.48 ml) in chlorosulphonic acid (25 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 acid and of bromine were destroyed with sodium hydrogen carbonate and sodium disulphite respectively. Extraction with ether and work-up in the usual way provided an orange oil (25.5 g) which after distillation (176° and 0.1 mmHg) and chromatography (alumina, grade IV, neutral; elution with light petroleum) provided (+)-3,3,8-tribromocamphor (11) (13.4 g, 61%).

(+)-8-*Bromocamphor* (12).—(+)-3,3,8-Tribromocamphor (11) (5 g) was dissolved in cooled glacial acetic acid (25 ml). Zinc dust (2.67 g) was added and the mixture was stirred vigorously. The exothermic reaction subsided after 30 min and the solution was allowed to cool to room temperature over the next 0.5 h. The contents of the flask were decanted from the zinc salt into ether (200 ml). The ethereal solution was washed with water (10 × 50 ml) and dried. Removal of the solvent, followed by crystallisation of the solid (2.95 g) from light petroleum (b.p. 30—60°), provided (+)-8-bromocamphor (13),* m.p. 82—83 °C, identical (spectra) with an authentic sample.[1]

(+)-3,9,9-*Tribromocamphor* (13).—The synthesis of (+)-3,9-dibromocamphor (9; X = H, Y = Br) was completed by the literature method.[2a] Removal of solvent from the mother liquor obtained after crystallisation of (9; X = H, Y = Br) produced a white crystalline solid which was shown by g.l.c. and t.l.c. to be a mixture of 3,9-dibromocamphor and an unknown compound. Sublimation (140° and 0.01 mmHg) of the mixture followed by crystallisation

* (+)-3,3,8-Tribromocamphor has also been converted into (+)-8-bromocamphor by using zinc and hydrogen bromide in methylene chloride.[1]

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[15] C. J. Collins, V. F. Raaen, B. M. Benjamin, and I. T. Glover, *J. Amer. Chem. Soc.*, 1967, **89**, 3940.

of the light brown residue from acetone provided (+)-*3,9,9-tribromocamphor* (13), m.p. 198—199.5 °C; $[\alpha]_D^{25}$ +82.62° (*c* 1.45 in $CHCl_3$); $\nu_{max.}$ 1 754 cm^{-1}; τ($CDCl_3$) 8.78 (3 H, s), 8.64 (3 H, s), 7.19 (1 H, t, *J* 5 Hz), 5.29 (1 H, d, *J* 5 Hz), and 3.74 (1 H, s); *m/e* 392/390/388/386 (M^+) and 311/309/307 (M − 79, M − 81) (Found: C, 30.95; H, 3.35; Br, 61.4. $C_{10}H_{13}Br_3O$ requires C, 30.85; H, 3.35; Br, 61.65%). The structure of this compound was confirmed by *X*-ray crystallographic analysis.[4]

(−)-*1,7-Dibromo-4-dibromomethyl-3,3-dimethylnorbornan-2-one* (14).—In the preparation of (+)-3,3,8-tribromocamphor (11) by method (B) a solution of the crude product in mixed hexanes at −8 °C deposited crystals, recrystallisation of which from carbon tetrachloride provided pure (−)-*1,7-dibromo-4-dibromomethyl-3,3-dimethylnorbornan-2-one* (14), m.p. 127—127.5 °C; $[\alpha]_D^{25}$ −56.09° (*c* 1.770 in $CHCl_3$); $\nu_{max.}$ 1 770 cm^{-1}; τ($CDCl_3$) 8.62 (3 H, s), 8.47 (3 H, s), 7.68 (4 H, m, ABCD), 5.62 (1 H, s), and 3.96 (1 H, s); *m/e* 391/389/387/385 (M − 79, M − 81) (Found: C, 25.6; H, 2.65; Br, 68.3. $C_{10}H_{12}Br_4O$ requires C, 25.65; H, 2.6; Br, 68.35%). The structure of this compound was confirmed by *X*-ray crystallographic analysis.[4]

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