NOTES

The Asymmetric Synthesis of (−)-Menthol and (−)-Isomenthol by the Hydroboration of (±)-3-*p*-Menthene

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Brown and Zweifel¹⁾ recently reported that the hydroboration of olefins with diisopinocampheylborane resulted in a nearly complete asymmetric synthesis of the corresponding alcohols. On the basis of the steric course proposed,²⁾ it should be possible to perform an asymmetric synthesis of (−)-menthol and (−)-isomenthol by means of the hydroboration of (±)-3-*p*-menthene with (+)-monoisopinocampheylborane derived from (−)-(1S : 5S)-α-pinene.

We wish here to report such a synthesis.

Because of the feeble reactivity of the trisubstituted ethylene bond in 3-*p*-menthene toward dialkylborane, the monoisopinocampheylborane was preferred here as the asymmetric hydroboration reagent to the usual diisopinocampheylborane. 2.1 g. of (−)-α-pinene ($[\alpha]_D^{20}$ −34.7°; 68% optical purity), (0.015 mol.)), and 0.8 g. of sodium borohydride were dissolved in 15 ml. of dry diglyme at room temperature; to this solution there was then stirred, drop by drop, 3.0 g. of boron trifluoride etherate (47% BF_3 content) under a nitrogen stream over a 30-min. period. The disappearance of pinene was checked from time to time by g. l. c. (±)-3-Menthene (2.1 g.) (0.015 mol.) was added to the isopinocampheylborane, and, after the completion of the reaction (2 hr.), the reaction mixture was treated with 3 N sodium hydroxide and a 30% hydrogen peroxide solution. After 16 hr., this was worked up as usual. The separation of the product by g. l. c. yielded (−)-menthol, $[\alpha]_D^{20}$ −6.9° (chloroform), optical purity 14%, 0.57 g. (24.4% based on 3-menthene), (−)-isomenthol, $[\alpha]_D^{20}$ −13.4° (chloroform), optical purity 56%, 1.03 g. (44.0%) and (+)-isopinocampheol, $[\alpha]_D^{20}$ +22.1° (chloroform), 1.82 g. Both (−)-menthol and (−)-isomenthol were identified by a comparison of their n_D, IR,

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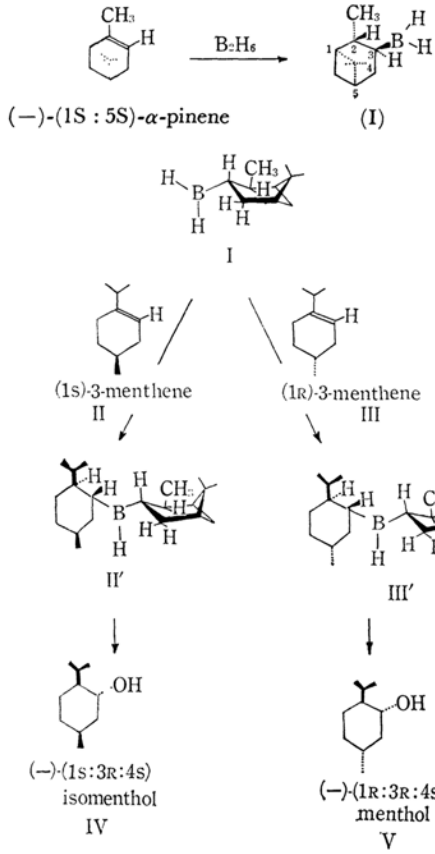
1) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 486 (1961).

2) H. C. Brown, N. R. Ayyanger and G. Zweifel, ibid., **86**, 397 (1964).

and R^t values with those of authentic specimens.

Of the various conceivable anti-Markownikoff-*cis*-additions of the boron-hydrogen bond of (+)-monoisopinocampheylborane (I) to the double bond in both (1S)-3-menthene (II) and (1R)-3-menthene (III), the attack of I, with the less bulky C_4-methylene grouping of the isopinocampheyl moiety oriented in the front, as is illustrated, to the rear sides of both II and III should be sterically more favored than those occurring in the opposite direction. This accounts for the experimental results which show that (−)-(1S : 3R : 4S)-isomenthol and (−)-(1R : 3R : 4S)-menthol were obtained preponderantly over their respective dextrorotatory enantiomers, which would be expected from the attack of I on the front side of III and II. Moreover, an inspection of the Stuart model of III reveals considerable steric interference between the (1R)-methyl group of III and the C_4-methylene grouping of the (+)-isopinocampheyl moiety, while this is not the case with II′, where the (1S)-methyl group is kept away from the C_4-methylene of I. The situation is just reversed in the less favored attack occurring on the rear side of I. This accounts for the higher optical yield of (−)-isomenthol (IV) and the lower optical purity of (−)-menthol (V).



In carrying out the conversion of (±)-3-*p*-menthene to racemic menthol by hydroboration with diborane, Ascoli[3] observed that the total yield of hydroxylic compounds was lower, the larger the ratio of menthol to isomenthol. This was ascribed to the higer oxidation-hydrolysis rate of menthylborane as compared with that of isomenthylborane. However, the (−)-menthol/(−)-isomenthol ratio (1 : 1.8) observed in our asymmetric synthesis, in which oxidation-hydrolysis was completely effected, may also be interpreted in terms of the rate of the formation of the intermediates, II′ and III′, from II and III respectively.

Studies of the asymmetric hydroboration of other monoterpeneolefins are currently in progress in our laboratories; they will be described elsewhere in detail.

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[3] F. Ascoli, A. M. Liquori and B. Pispia, *Chem. Ind.*, **1964**, 1579.