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THE DEBROMINATIVE REDUCTION OF 2-BROMOISOPINOCAMPHONE WITH METAL HYDRIDES

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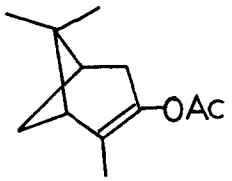
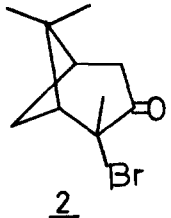
Although the action of metal hydrides on α-haloketones generally leads to halohydrins (1) a number of exceptions have been reported. In these, the debrominated ketone has been obtained instead (2). We wish to report here the results of the hydride reduction of a bromoketone which yields almost exclusively debrominated products. Bromination of the enol acetate 1 yields 2-bromoisopinocamphone, 2 (3). Reduction of

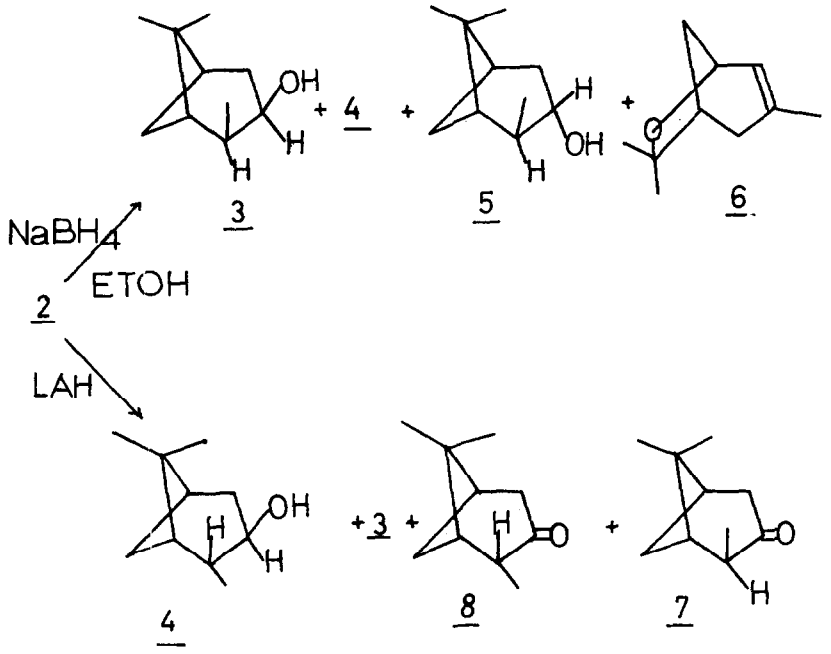


1



2

the latter with a large excess of sodium borohydride in 95% ethanol gave no detectable bromohydrin. The product mixture contained, however, 73% (4) of neoisopinocampheol, 3, identified by comparison of its NMR spectrum to that reported for 3 (5), by stereospecific oxidation to isopinocamphone (5) and by its lack of identity (g.c. retention time) with an authentic

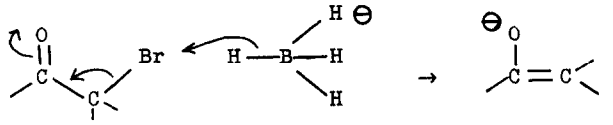


sample of the epimeric alcohol, isopinocampheol, 5. Another alcohol component of the product mixture, present in 17%, consisted of approximately equal quantities of neopinocampheol, 4, and isopinocampheol, 5. A fourth product, 10%, was shown to be the bicyclic ether pinol by spectral and g.c. retention time comparisons with an authentic sample.

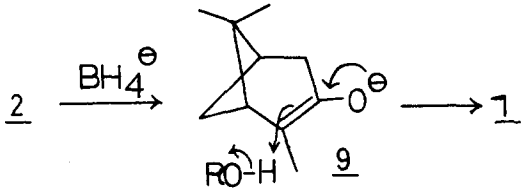
Reduction of 2 with excess lithium aluminum hydride also resulted in completely debrominated material. The stereochemical result, moreover, is different from the one described above for borohydride reduction. The reaction mixture in this case consisted of an alcohol fraction, 73%, containing 3 and 4 in

the ratio 1:5 and a ketone fraction, 20%, containing 7 and 8 in the ratio 3:2. The remainder of the product mixture 7% was highly volatile material which was not characterized.

The mechanism of borohydride debromination of an α-bromoketone has been suggested (2a) to precede via the enolate:



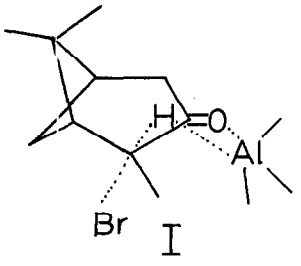
Our results from 2-bromoisopinocamphone are compatible with this concept since the initially formed enolate, 9, should undergo irreversible protonation from the least hindered side (6) to yield isopinocamphone.



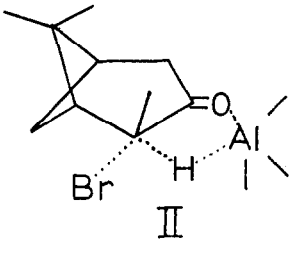
Reduction of the latter with the excess hydride present would then be expected to yield the neoiso compound 3. An alternative mechanism, however, is suggested by our results with lithium aluminum hydride in ether. Under these conditions if the enolate 9 were to be formed the reaction would cease at this stage (7) to yield on work up some mixture of the ketones 7 and 8≠. That the alcohols, 3 and 4 are obtained from lithium

≠ A preliminary experiment with a limited quantity of lithium aluminum hydride indicates that all four products are formed before disappearance of the bromoketone 2.

aluminum hydride suggests that some other pathway must be followed here. It is suggested that the first step in these reductions is the direct displacement of bromide by either of the transition states, I or II.



I

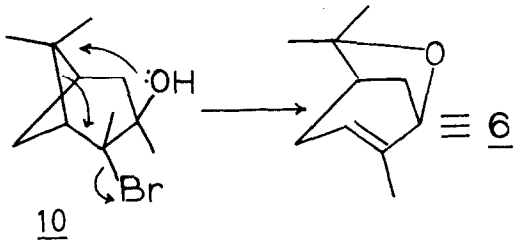


II

It is interesting to note that the configuration ratio, 1:3, of the 2-methyl group in the over-all reduction mixture, 3 + 7 : 4 + 8, resembles the equilibrium ratio, 1:4, of the isomeric ketones 7 and 8 (5). If the possible transition states I and II resemble products then the reduction would be expected to produce the pino-compounds predominantly since in this series the 2-methyl group is trans to the gem dimethyl bridge. Debromination with lithium aluminum hydride appears to be, like ketones in many cases, subject to "product development control" (8). In contrast the debrominative reduction with borohydride, if it occurs by direct displacement, should be subject to "steric approach control" (8) since the bulk of the solvated reagent would prevent its attack from the topside of 2.

It is not at present clear why debromination competes so favorably with ketone reduction in this system. One of the products obtained in the borohydride reduction, however, is clearly derived from the bromohydrin 10. Apparently the latter

rapidly rearranges to pinol via a mechanism such as;



10 ≡ 6

ACKNOWLEDGMENTS

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4. The yields are given as percentages of the volatile products detected by gas chromatography.

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