

EPIMERIZATION IN THE  $\text{NaBH}_4$  REDUCTION OF ASYMMETRIC KETONES

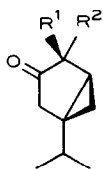
V. Hach<sup>1</sup>, Elizabeth C. Fryberg and Elizabeth McDonald

MacMillan Bloedel Research Ltd., Vancouver, B.C., Canada

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Accepted textbooks<sup>2,3</sup> claim that little, if any, epimerization or racemization is observed during  $\text{NaBH}_4$  reductions of ketones containing an asymmetric carbon atom adjacent to the C=O group undergoing reduction. The reasons for this have been aptly summarized by House<sup>2</sup> who, in summary, concludes that enolization necessary for racemization or epimerization is either insufficient or completely absent due to low basicity of the borohydride anion in solvents currently utilized in borohydride reductions.

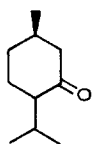
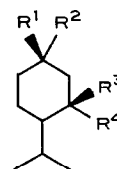
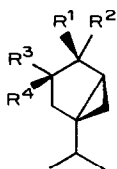
We now wish to report results showing that in preparative  $\text{NaBH}_4$  reductions of asymmetric ketones such an epimerization may readily occur at a rate higher than the rate of reduction. Consequently, the epimeric ketone is formed prior to the reduction which then gives rise to all four isomeric alcohols instead of the two expected. In our studies on the isomeric thujones<sup>4</sup> (I, II) and menthone VII we found that epimerization or its absence, and thus the outcome of reduction in regard to the number of stereoisomeric thujanols (III, IV, V, VI) and menthols (VIII, IX, X, XI) formed, are dependent on the presence or absence of small amounts of water in solvents used for  $\text{NaBH}_4$  reductions. Indeed, we are inclined to think that, under specific conditions of reduction and in similarly constituted ketones, concurrent epimerization or racemization will be the rule and not the exception.



I (+)-3-THUJONE



II (-)-3-ISOTHUJONE H CH<sub>3</sub>



VII (±) MENTHONE

	$\underline{R^1}$	$\underline{R^2}$	$\underline{R^3}$	$\underline{R^4}$	
III (+)-3-THUJANOL	CH <sub>3</sub>	H	OH	H	VIII MENTHOL
IV (+)-3-NEOTHUJANOL	CH <sub>3</sub>	H	H	OH	IX NEOMENTHOL
V (-)-3-NEOISOTHUJANOL	H	CH <sub>3</sub>	OH	H	X ISOMENTHOL
VI (-)-3-ISOTHUJANOL	H	CH <sub>3</sub>	H	OH	XI NEOISOMENTHOL

Our current interest in thujone chemistry has led to extensive studies on the reduction of I and II. In this connection we attempted to duplicate the recent work of Banthorpe and Davies<sup>5</sup> who reported the  $\text{NaBH}_4$  reduction of (-)-3-isothujone II in, presumably 100%, diglyme or ethanol to give only a mixture of alcohols V and VI (approximate ratio 6:4) and the analogous reduction of (+)-3-thujone I to give only III and IV (approximate ratio 4:6).

We carried out the reduction of (+)-3-thujone I in diglyme as described by Banthorpe et al<sup>5</sup> and to our surprise found that the product consisted of all four thujanols, III-VI. A similar result was obtained when (-)-3-isothujone II was reduced; all four alcohols were formed.

This unexpected observation prompted a detailed study on the  $\text{NaBH}_4$  reduction of ketones I and II and later included VII. The solvent range was expanded to include ethanol, 1-propanol and 2-propanol. Scrupulous attention was paid to the water content of the solvents studied. This aspect is generally considered to be of little relevance because of the relative stability of  $\text{NaBH}_4$  towards water. However, to our mind, water seemed to be the only factor which could possibly explain the discrepancy between Banthorpe's and our results.

Indeed, in dry alcohols and diglyme, less than 0.02%  $\text{H}_2\text{O}$  present, extensive epimerization precedes reduction, as shown in the following table which summarizes results from several experiments of the many carried out.

Starting Ketone	Solvent	Reaction Time Hr.	% of Thujanols Formed			
			III	IV	V	VI
(+)-3-Thujone	2-Propanol	4	33	32	22	13
	2-Propanol, 10% $\text{H}_2\text{O}$	4	63	37	--	--
	Ethanol, 5% $\text{H}_2\text{O}$	4	54	46	--	--
(-)-3-Isothujone	2-Propanol	4	23	24	33	20
	2-Propanol, 10% $\text{H}_2\text{O}$	4	--	--	59	41
	Diglyme	48	12	13	42	32

All reductions were carried out with 1 g of ketone in 10 ml solvent using 3H-equivalents of  $\text{NaBH}_4$  added at room temperature over a period of 3 hr. Magnetic stirring was applied throughout the experimental series. Experiments in anhydrous solvents were run with precautions usual for moisture-free reactions. Example of a kinetic-like run is given in the following table. Two grams of (+)-3-thujone I in 20 ml of dry 2-propanol were reduced at room temperature with 3 H-equivalents of  $\text{NaBH}_4$  added in one lot. An analogous experiment in 1-propanol showed the rate of reduction to be about three times higher than in 2-propanol, whereas the rate of epimerization was about the same. Therefore, throughout the time profile the total percentage of epimerized products, i.e. II, V and VI was lower than in 2-propanol.

Reaction Time Min.	Composition of Reaction Mixture					
	% Thujone		% Thujanol			
	I	II	III	IV	V	VI
15	70	2	14	11	2	1
30	51	6	21	17	3	2
60	39	9	24	20	5	3
120	19	10	28	23	12	6
240	9	4	33	26	18	10

The two thujones I and II are rather untypical ketones due to the internal strain of the bicyclohexane ring system<sup>6</sup> and the presence of the cyclopropane ring which contributes to various anomalous reactions of this system.<sup>7</sup> Therefore, it was only appropriate to investigate an asymmetric ketone free of such interferences. Menthone VII was the obvious choice. Experiments analogous to those described above were carried out and results obtained confirmed fully observations made in the thujone series. Reduction in anhydrous media led to the formation of all four menthols viz. VIII-XI; in the presence of water only menthol VIII and neomenthol IX were formed as expected. However, comparing results obtained under similar reaction conditions, it appears that the reduction rate of menthone is higher and thus the extent of epimerization lower than with either of the two thujones. The total of isomenthol series alcohols X and XI formed is only about 50% when measured as percentage of products attainable by complete equilibration of epimers.<sup>8</sup>

Certainly, the key question then is: What is the percentage limit of water that will prevent epimerization? We found that in the type of experiments tabulated and particularly in detailed experiments with menthone in 2-propanol, the critical point was between 1 and 2% H<sub>2</sub>O. With 1% H<sub>2</sub>O in 2-propanol the amount of epimerized products is, in broad terms, about 1/4-1/2 of the amount obtained in dry solvent. With 2-3% H<sub>2</sub>O the extent of epimerization fell into the limits of unambiguous detectability by GLC.<sup>9</sup> Obviously, these values may vary with the amount, ratio and mode of addition of NaBH<sub>4</sub>. We would suggest that the addition of 5% of water may be a safe precaution to prevent epimerization if so desired.

Previous work<sup>5,10,11,12</sup> has shown that the epimerization of thujones I and II and menthone VII can be achieved by the action of strong bases like sodium alkoxides or hydroxide. Interpretation of our results necessitates the postulation of a strong base to be present in the reducing system.<sup>13</sup> This may come about only by the interaction of NaBH<sub>4</sub> with the solvent system. The generation of a strong base from NaBH<sub>4</sub> and 2-propanol has recently been proposed by Johnson and Rickborn<sup>14</sup> in order to accommodate results of their studies. These authors observed another unprecedented and extensive side reaction in NaBH<sub>4</sub> reduction, viz. the Michael-type addition of the isopropoxide moiety to the double bond of conjugated aldehydes and ketones prior to their reduction. As in our case, this side reaction was suppressed by the presence of water, though Johnson and Rickborn did not attempt to define its minimum necessary percentage. Also, these authors presented a detailed and pertinent discussion on the mechanism of strong base formation in the NaBH<sub>4</sub> - 2-propanol system which we can only subscribe to.

Although our observations are, as yet, limited to the thujones and menthone, we would expect the epimerization by  $\text{NaBH}_4$  in anhydrous alcohols and diglyme to be operative with other asymmetric ketones as well, certainly with ketones whose enolizability is similar to that of ketones studied here. In regard to this it may be useful in experimental descriptions to specify, where applicable, the amount of water present in such reductions.

#### REFERENCES AND NOTES

1. Present address: Department of Chemistry, University of British Columbia, Vancouver 8, B.C. Part of the work reported here was completed at this institution. The hospitality of Professor J.P. Kutney is gratefully acknowledged. This work was supported, in part, by a National Research Council of Canada grant. We appreciate the permission given by the management of MacMillan Bloedel Research Ltd. to publish this paper.
2. H.O. House, *Modern Synthetic Reactions*, W.A. Benjamin, New York-Amsterdam, 1965, pp. 28-29.
3. N.G. Gaylord, *Reduction with Complex Metal Hydrides*, Wiley Interscience, New York, 1956.
4. We adopted the thujone-thujanol nomenclature proposed by H.C. Brown<sup>10</sup>.
5. D.V. Banthorpe and H.ff.S. Davies, *J. Chem. Soc. (B)*, 1356 (1968).
6. S. Chang, D. McNally, S. Shary-Tehrany, M.J. Hickey and R.H. Boyd, *J. Amer. Chem. Soc.*, **92**, 3109 (1970).
7. K.B. Wiberg in *Advances in Alicyclic Chemistry*, Vol. 2, Academic Press, New York-London, 1968, pp. 185-254.
8. Upon complete equilibration a (+)-3-thujone to (-)-isothujone ratio of about 35:65 respectively is attained. Similarly, the menthone-isomenthone ratio is about 70:30 respectively. See ref. 11 and 12 and literature cited therein.
9. Major part of GLC analyses was carried out under the supervision of Mr. K.L. McDonald. For details see: *J. Chromatographic Science*, in press.
10. S.P. Achakya, H.C. Brown, A. Suzuki, S. Nozawa and M. Itoh, *J. Org. Chem.*, **34**, 3015 (1969).
11. V. Hach, R.W. Lockhart, D. Cartlidge and E.C. McDonald, *Can. J. Chem.*, in press.
12. R.P. Bell and B.G. Cox, *J. Chem. Soc. (B)*, 194 (1970).
13. We appreciate the valuable comments made by Professor H.C. Brown.
14. M.R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).