REDUCTION OF TROPINONE

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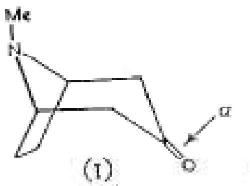
As part of a wider investigation into the stereochemistry of addition to heterocyclic ketones to yield isomeric alcohols, the reduction of tropinone has been studied. In Table I a summary of these results is presented. The tropine, ψ-tropine and tropinone content of the reaction products (> 90% yields) were separately determined by infrared analysis; the sum of these values for each mixture corresponded closely with the total base content (calc. as the amino-alcohol) determined by titration in non-aqueous media.[1]

Certain results are at variance with those given in the literature [lithium aluminium hydride is reported to yield ψ-tropine (isolated as the picrate) quantitatively;[2] aluminium *iso*propoxide is stated to reduce tropinone stereospecifically to ψ-tropine[3]].

Recently Dauben *et al.*[4] have shown that reduction of alkyl*cyclo*hexanones gives increasing proportions of the *cis* (less stable) isomers as the reagent is changed in the order $LiAlH_4$, $NaBH_4$, $Al(OPr^i)_3$. An increasing effective size of reducing species is presumed in the above order; this favours attack from the least hindered side of the carbonyl group (" steric approach control "), assuming an increasingly important role compared with the molecular energetics of product formation (" product development control ") subsequent to metallo-complex formation.

The results quoted in Table I may be explained as follows. If tropinone has the conformation (I) in all the solvents used, an increase in size of the reducing species will favour addition from side " *a* " to yield tropine; product development control will favour ψ-tropine production.



(I)

It is reasonable to assume that the latter factor will not vary greatly with solvent or reagent [e.g. equilibrations using sodium in *n*-amyl alcohol, or aluminium *iso*propoxide in *iso*propanol (or reductions using sodium in ethanol or *iso*butanol) give results which are virtually identical]. Increase in tropine content of the reduction products as the reagents are changed in the order sodium borohydride/water, lithium aluminium hydride/ether and aluminium *iso*propoxide/*iso*propanol indicates an increase in size of reducing species. A change in solvent may alter the effective size of reducing species, e.g. the results indicate that $NaBH_4$/absolute methanol > $LiAlH_4$/ether > $NaBH_4$/89% methanol-water > $NaBH_4/H_2O$. Presumably $NaBH_4$ behaves as a methoxyborohydride in methanol[5] and this may explain why, in Dauben's experiments, $NaBH_4$ has a larger effective size than $LiAlH_4$; (however, some water was present in the methanol during their $NaBH_4$ reduction).

References

[1] Beckett, A. H. and Tinley, E. H., " Titration in Non-Aqueous Solvents " (Poole, England: B.D.H., Ltd.)

[2] Mirza, R., *Nature, Lond.*, 1952, **170**, 630

[3] Kovacs, O (cited by Foder, G.), *Acta. Chim. Acad. Sci. Hung.*, 1955, **5**, 396

[4] Dauben, W. G., Fonken, G. J. & Noyce, D. S., *J. Amer. chem. Soc.*, 1956, **78**, 2579

[5] Gaylord, N. G., " Reduction with Complex Metal Hydrides," 1956, p. 18 (London: Interscience Publishers Ltd.)

Table I *Isomeric Composition of Mixtures of Tropine and ψ-Tropine (and Tropinone) upon Reduction of Tropinone*

Reducing Agent and Solvent		*Time (Hours)*	*Temp. °C*	*Percentage*			*Total Base Content (%)*	
				ψ-Tropine	*Tropine*	*Tropinone*	*A*	*B*
$LiAlH_4$	ether	0·5	reflux	54	45	1	96	97
	ether	5	reflux	54·5	45·5	—	92	97
$NaBH_4$	water	2	20	65	34	1	87	89
	water	48	reflux	69	30	1	95	94
	89%$MeOH/H_2O$	16	20	60	40	—	94	97
	95%$MeOH/H_2O$	6	reflux	51	49	—	99	98
	100%MeOH	6	reflux	48	52	—	92	94
	*iso*propanol	2·25	reflux	67	33	—	98	97
$Al(O\text{-}Pr.)_3$	*iso*propanol	1·5	82	29[a]	71	—	92	91
Na/C_2H_5OH +	toluene	3	reflux	85	11	4	95	95
Na/*iso*butanol + toluene		3	reflux	88	9	3	94	93
$Al(O\ Pr^i)_3$ equilibration from ψ-tropine.[b]		288	reflux	88	11	1	93	92
Na/amyl alcohol equilibration from tropine[b]		12	reflux	91	8	1	96	93

A Total base content of mixture (%) as sum of infrared determined values.
B Total base content of mixture (%) by titration in non-aqueous media.
a Figure slightly higher than true value since slow equilibration occurs subsequent to amino-alcohol production.
b Equilibration of other isomer gave similar results.