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STEREOCHEMISTRY OF THE REDUCTION OF TROPINONE

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Abstract—Tropinone has been reduced under various conditions of time, temperature, solvent and reducing agent. The stereoisomeric composition of the reduction product was determined by infra-red spectrophotometry. The results indicate the participation of kinetic and thermodynamic factors in the stereoisomeric course of the reduction, the former depending upon the effective size of the reducing species. An assignment of the order of size of reducing species in particular solvents is made.

The stereoisomeric composition of the product of equilibration is independent of the reagent and the temperature in the system studied.

DURING a general investigation of the stereochemistry of addition to heterocyclic ketones, the stereochemistry of the reduction of tropinone using various reagents and conditions has been examined.

Analytical method. Other workers[1,2] have questioned the accuracy of the analytical procedures used for the analysis of the isomeric mixtures obtained on the reduction of ketones, the results of which have been used as the basis for generalisations on the stereochemistry of the additions to ketones. The infra-red spectrophotometric analytical procedure used in the present investigation constituted an accurate ($\pm$3 per cent) and rapid method for the assay of mixtures of tropine, ψ-tropine and tropinone. The infra-red absorption curves for tropine and ψ-tropine (Fig. 1) show peaks at 958 cm^{-1} and 1020 cm^{-1} respectively, which are free from interference from the other epimer. The assay procedure was based on these peaks (Fig. 2), other stronger peaks being rejected, since the use of these necessitated compensation for a sloping background interference which made the assay inherently less accurate. The tropinone content of the mixtures was determined by plotting a calibration curve (Fig. 3) at 1720 cm^{-1} under the same operating conditions as for the tropines. The absorptions at 958 cm^{-1} and 1020 cm^{-1} were corrected for interference from tropinone (Fig. 3). A check on the accuracy of the assay was obtained by measuring the absorption [E(1%/cm)] at 972 cm^{-1} and 990 cm^{-1}, which are not in the optimum optical density regions. The absorptions were plotted against the percentage tropine/ψ-tropine (tropinone absent) found in the assay. The graph (Fig. 4), the lines on which represent the theoretical absorption for tropine/ψ-tropine mixtures, indicates an accuracy of $\pm$5 per cent. Known mixtures of tropine and ψ-tropine gave results in all cases within the accuracy claimed for the assay. By summation of the quantities of tropine, ψ-tropine and tropinone the relative percentage of each present could be calculated. The recovery as indicated by infra-red absorption was in close agreement with the total base content, (calculated as amino-alcohol) of the mixtures as determined by non-aqueous titration.

[1] R. J. Wicker, *J. Chem. Soc.* 2165 (1956).
[2] E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.* **79**, 5992 (1957).

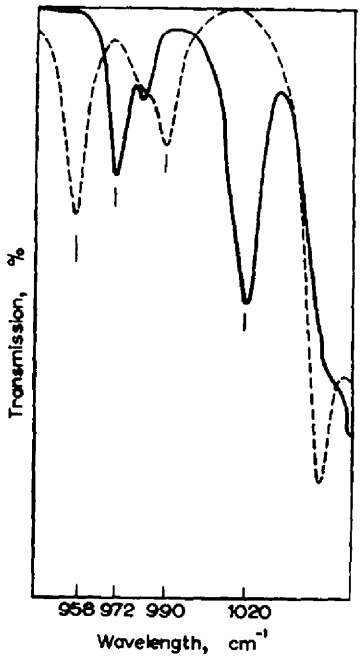


FIG. 1. Infra-red absorption curve for tropine and ψ-tropine in CS_2. (Tropine – – – –, ψ-tropine ——)

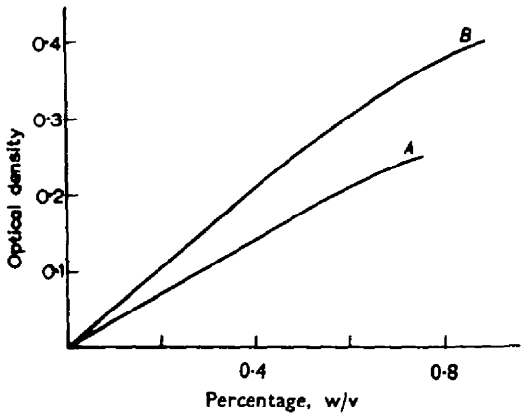


FIG. 2. Calibration curve of tropine (A, 958 cm^{-1}) and ψ-tropine (B, 1020 cm^{-1}).

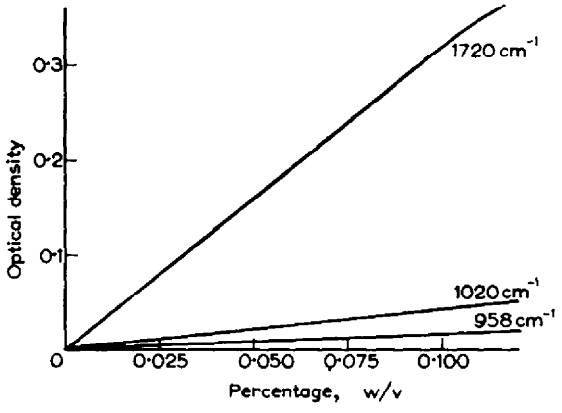


FIG. 3. Calibration curve of tropinone, showing corrections applied to epimeric alcohols for tropinone.

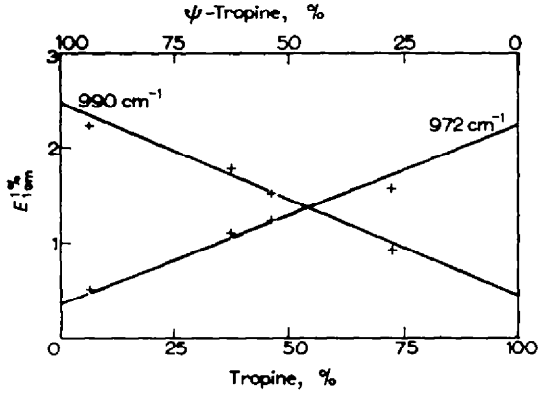


FIG. 4. Theoretical absorption for tropine/ψ-tropine mixtures (+ represents observed absorptions during assay process).

Attempts to determine the composition of the mixtures by chromatography on alumina proved tedious, and although less accurate than the results obtained by the infra-red procedure, qualitatively supported the latter.

Results. The results of the reductions of tropinone are summarised in Table 1.

The equilibration of tropine and ψ-tropine using sodium in *n*-pentanol and *iso*-butanol gave results equivalent with those obtained upon prolonged equilibration using aluminium *iso*propoxide in *iso*propanol; isomerisation involved in a 2·5 hour reduction with the latter reagent will not alter significantly the stereochemical composition of the product of reduction.

Equilibration did not occur using lithium aluminium hydride, sodium borohydride or potassium borohydride even at a temperature of approximately 100°.

The proportion of tropine in the reduction products increased as the following reagents were used: Na/ethanol or *iso*butanol; $NaBH_4$ or KBH_4/water; $NaBH_4$/89% v/v methanol; $LiAlH_4$/ether or tetrahydrofuran; $NaBH_4$/95% v/v methanol; $NaBH_4$ or KBH_4/methanol; $NaBH(OCH_3)_3$/methanol; $Al(OPr^i)_3$/*iso*-propanol.

Using $LiAlH_4$, the change of solvent from ether to tetrahydrofuran gave similar reduction mixtures (Table 1, nos. 1, 5). Changes of the temperature of reduction had negligible effect on the stereochemical course of the reaction using $NaBH_4$ (Table 1, nos. 7, 8), $LiAlH_4$ (Table 1, nos. 1, 5) and sodium in *iso*butanol (Table 1, nos. 26, 27). [Contrast Nace and O'Connor[3] who found that the isomeric composition upon reduction of cholestanone by $LiAlH_4$ and aluminium alkoxides was greatly affected by temperature, and Trevoy and Brown[4] who suggested that lower temperatures increased the "directive effect" on the $LiAlH_4$ reductions of 1:2-diketones].

DISCUSSION

Factors controlling stereochemistry of reduction

The variation in the stereoisomeric composition of the products of reduction of tropinone using various reagents and conditions is explicable in terms of thermodynamic and kinetic contributions in the reaction. This explanation is supported by various studies of additions to the carbonyl group of acyclic, alicyclic and polycyclic ketones,[2,3,5–15] e.g., Jackman *et al.*[5] considered that steric hindrance about the carbonyl group was the chief factor determining the relative amount of isomers obtained in the reduction of alkyl*cyclo*hexanones, Nace *et al.*[3] emphasised the size of the reducing agent in the reduction of cholestanone; both groups mentioned the importance of the relative thermodynamic stability of the isomers in certain cases. Barton[14] emphasised the thermodynamic factor in pointing out that the equatorial isomer was predominant in the product of reductions of alicyclic unhindered ketones. Dauben

[3] H. R. Nace and G. L. O'Connor, *J. Amer. Chem. Soc.* **73**, 5824 (1951).
[4] L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.* **71**, 1675 (1949).
[5] L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.* 2641 (1949).
[6] D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.* **72**, 5743 (1950).
[7] H. L. Goering and C. Serres, Jr., *J. Amer. Chem. Soc.* **74**, 5908 (1952).
[8] D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).
[9] D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.* **75**, 6005 (1953).
[10] R. Cornubert, G. Barrand, M. Cormier, M. Descharmes and H. G. Eggert, *Bull. Soc. Chim. Fr.* 400 (1955).
[11] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956).
[12] J. B. Umland and M. J. Jefraim, *J. Amer. Chem. Soc.* **78**, 2788 (1956).
[13] K. D. Hardy and R. J. Wicker, *J. Amer. Chem. Soc.* **80**, 640 (1958).
[14] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).
[15] J. B. Umland and B. W. Williams, *J. Org. Chem.* **21**, 1302 (1956).

TABLE 1.—ISOMERIC COMPOSITION OF MIXTURES OF TROPINE AND ψ-TROPINE (AND TROPINONE) UPON REDUCTION OF TROPINONE

Reducing agent	Temp.	Time (hr)	Percentage			Total base content %	
			ψ-Tropine	Tropine	Tropinone	A*	B*
1. $LiAlH_4$ ether	Reflux	0·5	54	45	1	96	97
2. $LiAlH_4$ ether	Reflux	5·0	54·5	45·5	—	92	97
3. $LiAlH_4$ ether (a)	Reflux	3·0	57	43	—	91	92
4. $LiAlH_4$ ether (b)	Reflux	1·0	56·5	41	2·5	91	93
5. $LiAlH_4$ tetrahydrofuran	Reflux	5·0	57	42	1	92	92
6. $NaBH_4$ water	20°	2·0	65	34	1	87	89
7. $NaBH_4$ water	20°	24·0	72	28	—	97	97
8. $NaBH_4$ water	Reflux	48·0	69	30	1	95	94
9. $NaBH_4$ water (c)	20°	2·0	70	29	1	97	99
10. $NaBH_4$ 25% v/v methanol	20°	7·0	68	32	—	87	85
11. $NaBH_4$ 89% v/v methanol	20°	16·0	60	40	—	94	97
12. $NaBH_4$ 95% v/v methanol	Reflux	6·0	51	49	—	99	98
13. $NaBH_4$ 100% v/v methanol	Reflux	6·0	48	52	—	92	94
14. $NaBH_4$ ethanol	Reflux	6·0	52	48	—	97	96
15. $NaBH_4$ *n*-butanol	Reflux	6·0	58	42	—	99	96
16. $NaBH_4$ *iso*propanol	Reflux	2·25	67	33	—	98	97
17. KBH_4 water	20°	24·0	66	34	—	92	93
18. KBH_4 methanol	Reflux	6·0	44	55	1	89	90
19. $LiBH_4$ tetrahydrofuran	Reflux	5·0	66	34	—	90	89
20. $NaBH(OCH_3)_3$ water	20°	24·0	54	39	7	82	88
21. $NaBH(OCH_3)_3$ water	Reflux	48·0	59	41	—	90	90
22. $NaBH(OCH_3)_3$ methanol	Reflux	6·0	37	59	—	94	96
23. $Al(OPr\textit{i})_3$ *iso*propanol (d)	Reflux	2·5	34	65	1	81	91
24. $Al(OPr\textit{i})_3$ *iso*propanol (d)	Reflux	1·5	29	71	—	92	91
25. Na/C_2H_5OH/toluene	Reflux	3·0	85	11	4	95	95
26. Na/*iso* C_4H_9OH/toluene	Reflux	3·0	88	9	3	94	93
27. Na/*iso* C_4H_9OH/toluene	0°	18·0	89	7	4	98	96
28. Na/*iso* C_4H_9OH/toluene	0°	18·0	84	10	6	96	96
29. $Al(OPr\textit{i})_3$ equilibration "Tropine" (e)	Reflux	20	36	60	4	86	90
30. $Al(OPr\textit{i})_3$ equilibration "Tropine" (e)	Reflux	40	54	43	3	90	88
31. $Al(OPr\textit{i})_3$ equilibration "Tropine" (e)	Reflux	288	83·5	16·0	0·5	102	95
32. $Al(OPr\textit{i})_3$ equilibration "Pseudotropine"	Reflux	40	93	6	1	96	96
33. $Al(OPr\textit{i})_3$ equilibration "Pseudotropine"	Reflux	288	88	11	1	93	92
34. Na/*n*-pentanol equilibration $LiAlH_4$ reduction product (f)	Reflux	3	84	15	1	92	93
35. Na/*n*-pentanol equilibration "Tropine" (e)	Reflux	12	91	8	1	96	93
36. Na/*n*-pentanol equilibration "Pseudotropine"	Reflux	12	88	11	1	92	92
37. Na/*iso*butanol equilibration Tropine	0°	18	14	81	5	86	91

(a) 4 moles $LiAlH_4$: 1 mole tropinone.
(b) ¼ mole $LiAlH_4$: 1 mole tropinone.
(c) Inverse addition.
(d) Figure slightly higher than true value since slow equilibration occurs subsequent to amino-alcohol production.
(e) "Tropine" containing 94% tropine and 6% ψ-tropine.
(f) $LiAlH_4$ reduction product 2.
A*—Total base content of mixture (%) as sum of infra-red determined values.
B*—Total base content of mixture (%) by titration in non-aqueous media (calc. as amino-alcohol).

et al.[11] stated that increase in the effective size of the reducing agent resulted in "steric approach control" assuming an increasingly important role compared with the molecular energetics of product formation, "product development control."

(a) *Thermodynamic factor.* A method of allocation of the relative thermodynamic stabilities of epimeric alcohols involves the measurement of their percentages in the mixture obtained under "equilibrating conditions". The relative importance of factors other than thermodynamic in the reduction of the parent ketone is thus assessed from the departure of the isomeric content of the reduction product from the "equilibrated" values (usually sodium/alcohol equilibration).* Two assumptions are inherent in this treatment, (i) that the difference in energy levels of the isomers under equilibrating conditions does not differ greatly from the difference of the activation energies of the complex of the two forms involved in reduction, and (ii) that differences in equilibrating conditions do not alter the stereoisomeric composition of the product. It seems reasonable to assume however, that changes in the equilibrating conditions may in fact alter the position of equilibration since solvation and alcohol–reagent interaction may alter the apparent relative sizes of the alcoholic group or anion in the two conformations and thus their relative thermodynamic stabilities. The temperature of equilibration could also affect the stereochemical composition. Recently Eliel and Ro[2] have shown that while aluminium *iso*propoxide equilibration of 4*t*-butyl*cyclo*hexanol gave 77–81 per cent of the more stable *trans* isomer, $LiAlH_4$ reductions gave an even greater proportion (91–93 per cent), a case in which the above assumptions would appear to be invalid. Umland and Williams[15] for instance report that reduction of 2-methyl*cyclo*pentanone with sodium in alcohol and equilibration of the alcohol with aluminium *iso*propoxide gave different results (see also Huckel[16]); Hardy and Wicker[13] consider that reduction with sodium in alcohol will not always yield the "equilibration mixture" and have stressed the importance of the temperature of the reduction.

The present investigation of the equilibration of tropine and ψ-tropine indicates that different reagents, e.g. aluminium *iso*propoxide in *iso*propanol and sodium in *n*-pentanol (Table 1, nos. 33, 36) give products of similar composition which are in general agreement with the isomeric ratios obtained by the sodium in ethanol or sodium in *iso*propanol reductions of tropinone. Furthermore, Na/alcohol reduction of tropinone at different temperatures gives similar results. It would appear reasonable to assume that the results indicate that equilibration of the ions or the alcohols *per se* is involved and that the effect of the reagent is catalytic.

Equilibration is assumed to proceed via dehydrogenation to an intermediate ketone (or aldehyde) and subsequent reduction.[17,18] In one instance, the intermediate ketone has been shown to be formed in the reaction[19] and Doering and Aschner[20] found that equilibration of (−)-phenylmethylcarbinol using potassium *t*-butoxide was completely inhibited by the exclusion of oxygen, potassium peroxides and carbonyl

*An alternative approach to this problem is to assume that the equilibration results are only a qualitative measure of a directional effect. This directive effect is initiated at the first instant of attack of the C atom of the carbonyl group by the reagent and it may well reflect the difference in energy required to direct the forming $C{-}O^-$ moiety into either of the two alternative conformations.

[16] W. Huckel, *Liebigs Ann.* **533**, 1 (1937).

[17] T. Wagner-Jauregg, *Freudenberg, Stereochemie* p. 866. Franz Deuticke, Leipzig (1932).

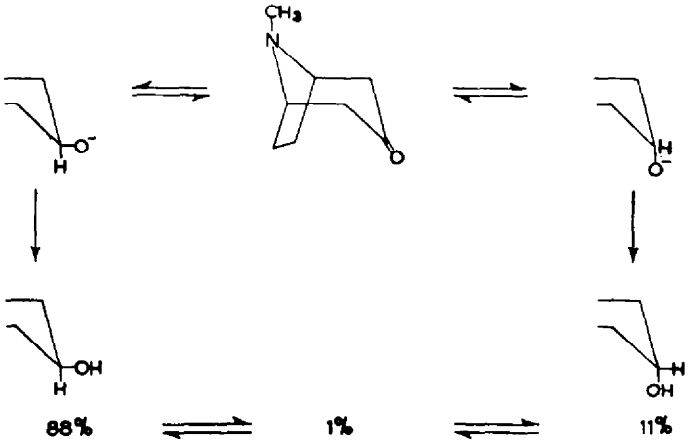
[18] W. Huckel, *Theoretische Grundlagen der Organischen Chemie* Vol. I, p. 286. Akademische Verlagsgesellschaft, Leipzig (1934).

[19] W. Huckel and H. Naab, *Ber. Dtsch. Chem. Ges.* **64**, 2137 (1931).

[20] W. von E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.* **71**, 838 (1949).

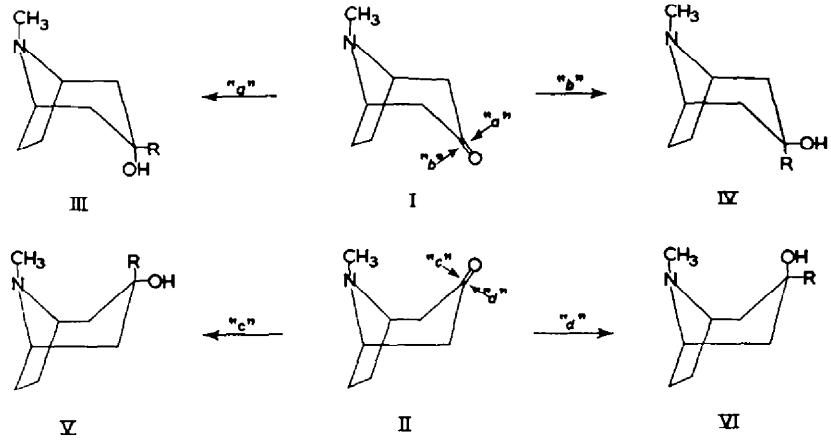
compounds, but that addition of oxidation–reduction systems caused rapid equilibration. In the present work, the ketone (tropinone) has been proved to be present in the products of equilibration of tropine and ψ-tropine using sodium/*n*-pentanol or aluminium *iso*propoxide as equilibrating reagents. (Table 1, nos. 31, 33, 35 and 36).

Since the stereoisomeric proportions are unaffected by the reagents, equilibration of the epimeric alcohols from tropinone may be represented as:—



(b) *Kinetic factor.* The conformation of tropinone in the reaction, the solvent and its effect on the size of the reducing species, the type of the reagent and its mechanism of reaction with the ketone may be considered as potential contributors to the kinetic factor in the reduction.

It seems reasonable to assume that tropinone will exist in a state of dynamic equilibrium between the chair (I) and the boat (II) conformations with probably (I) in major amount. Models indicate that reaction in conformation (I) would result in attack from side "b" being sterically hindered due to the methylene bridge with the resultant kinetic control strongly favouring the production of an alcohol with the hydroxyl group in the tropine conformation (III). Tropinone in conformation (II) would slightly favour attack from side "d" with a consequent kinetic control favouring the predominant formation of the ψ-tropine type alcohol.



The rate controlling step in the addition of an organometallic reagent to a ketone is considered to be attack of the R^- on the carbon of the carbonyl group. Although full clarification of the mechanism of reduction by complex metal hydrides and alkoxides has not yet been established, there is general agreement that the rate controlling step in reduction is attack by an H^- on the carbonyl carbon. Due to this similarity of mechanism, it would appear reasonable to use as evidence for the conformation of tropinone under nucleophilic attack, the fact that the reaction of phenyl lithium on tropinone gives only one isomer (97%).[21–23] The infra-red spectrum of this alcohol indicates the tropine-type character of the hydroxyl group (type of absorption and lack of intramolecular hydrogen bonding), which establishes that tropinone must have reacted in the chair conformation.

In the reduction of tropinone, steric factors will result in attack from side "a" being less hindered than that from side "b"; however attack from side "a" will require a higher activation energy since the resulting anionic complex will be developed in the thermodynamically less stable axial conformation. Increasing size of reducing species will therefore favour addition to side "a" to yield tropine, if the differences in the activation energies of the two sides of attack upon the carbonyl group are approximately represented by the differences in the energy levels obtained during equilibration. [If the carbonyl oxygen is co-ordinated to a moiety of the reducing agent, i.e. BR_3 of $NaBHR_3$ (or AlH_3 of $LiAlH_4$), increasing size of the co-ordinated group will favour anion formation in the more stable conformation. The formation of a higher proportion of tropine in the reduction product as R is changed from H to OCH_3, indicates that the steric control of the direct attack upon the carbonyl carbon plays a much more important role than carbonyl oxygen co-ordination.]

Reagents and solvents. The order of effective reducing species size of the reagents and solvents suggested from consideration of the stereoisomeric results quoted in Table 1 is $Al/OPr^{iso})_3$/*iso*propanol > $NaBH(OCH_3)_3$/methanol > $NaBH_4$/methanol > $LiAlH_4$/ether > $NaBH(OCH_3)_3$/water > $NaBH_4$/water. This differs from the order given by Dauben *et al.*[11] [$Al(OPr^{iso})_3 > NaBH_4 > LiAlH_4$] for reduction of 2- and 4-alkyl*cyclo*hexanones. This difference probably arises because these workers did not appear to fully consider the effect of solvent upon the reducing species size; certain anomalies also appear in the published results for the isomeric contents which formed the basis of their conclusions, e.g. the value of 82 per cent *trans*-isomer upon reduction of 2-methyl-*cyclo*hexanone with $LiAlH_4$, since values of 64[6,13] and 60[24] per cent have been reported.[11] A value of 88 per cent, *trans*-isomer in the equilibration of 4- methyl*cyclo*hexanol was used,[11] but Eliel and Ro[2] report a result of 69 and 71 per cent using an infra-red analytical procedure which appears to be inherently more accurate.

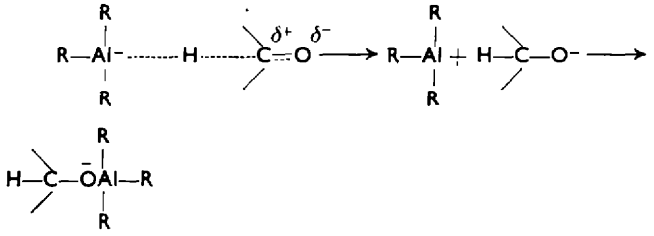
Since the effective reducing species size is the controlling kinetic factor, interaction (either physical or chemical) between the solvent and the reducing agent becomes important. The formation of etherates of $LiAlH_4$[25] and $LiBH_4$[26,27] has been established,

[21] A. H. Beckett, A. F. Casy, G. Kirk and J. Walker, *J. Pharm. Pharmacol.* **9**, 939 (1957).
[22] A. C. Cope and A. A. D'Addieco, *J. Amer. Chem. Soc.* **73**, 3419 (1951).
[23] S. Archer and T. R. Lewis, *Chem. & Ind.* 853 (1954).
[24] A. K. Macbeth and J. S. Shannon, *J. Chem. Soc.* 2852 (1952).
[25] N. G. Gaylord, *Reduction with Complex Metal Hydrides.* Interscience. New York (1956).
[26] G. W. Schaeffer, T. L. Kolski and D. L. Ekstedt, *J. Amer. Chem. Soc.* **79**, 5912 (1957).
[27] T. L. Kolski, H. B. Moore, L. E. Roth, K. J. Martin and G. W. Schaeffer, *J. Amer. Chem. Soc.* **80**, 549 (1958).

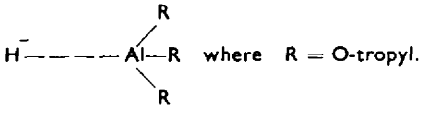
while $NaBH_4$ can be solvated.[28] Little attention appears to have been given to the effect of solvent although Dauben *et al.*[29] have suggested that the solvent may affect the stereochemical composition of the reduction product using $LiAlH_4$.

In the present investigation, it has been established that the solvent will affect the isomeric composition of the reduction product to the greatest extent where chemical reaction between reagent and solvent occurs to produce a new reducing species.

Lithium aluminium hydride. Reduction of a ketone with $LiAlH_4$ is considered to proceed as follows:—



The fact, that a $\frac{1}{4}$ mole $LiAlH_4$ reduces tropinone completely and gives the same isomeric ratio as reduction with 4 moles $LiAlH_4$ indicates not only that all the hydrogen atoms of the reagent are used in the reduction, but also that as the R = H groups of $LiAlH_4$ becomes replaced by R = —O-tropyl groups, the reducing efficiency of the reagent is increased, excess $LiAlH_4$ playing a negligible part in the reaction. Since the size of the reagent increases as the reaction proceeds, one might expect the final reducing species to constitute a very large steric factor (e.g. the change from $NaBH_4$ to $NaBH(OCH_3)_3$ has a profound effect on the stereoisomeric ratio), but the results suggest that this is not the case. It is therefore concluded that in the transfer complex, the more highly substituted aluminohydride constitutes a smaller steric factor than that which its bulk suggests due to the greater ease with which the hydride particle can be transferred to the carbonyl carbon.[30] This may be envisaged as the "B strain" in (VII) leading to a facile H^- separation which leads to virtual non-participation of the aluminocomplex in the stereochemistry of reduction.



(VII)

Using sodium trimethoxyborohydride, the reduction is considered to involve the participation of the hydride ion in conjunction with the boron complex (see later).

Borohydride in various solvents:—The actual effective size of the reducing species using a borohydride reagent will depend upon the nature of the solvent since chemical interaction between the reagent and various solvents is known. The equivalence of the effective size of the borohydride reagent in water, tetrahydrofuran and *iso*propanol is indicated by the similar isomeric ratios obtained on reduction of tropinone in these solvents (Table 1, nos. 6, 16 and 19).

In the aqueous methanol system, increase in the methanol content gave an increase

[28] H. C. Brown, E. J. Mead and P. A. Tierney, *J. Amer. Chem. Soc.* **79**, 5400 (1957).
[29] W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, *J. Amer. Chem. Soc.* **78**, 3752 (1956).
[30] H. C. Brown, E. J. Mead and C. J. Sharp, *J. Amer. Chem. Soc.* **78**, 3616 (1956).

in the tropine content of the product (Table 1, nos. 10, 11, 12 and 13) indicating the participation of a larger reducing species, presumably the methoxyborohydrides, since $NaBH_4 + CH_3OH \rightarrow NaBH_3(OCH_3) + CH_3OH \rightarrow NaBH_2(OCH_3)_2 + CH_3OH \rightarrow NaBH(OCH_3)_3 + CH_3OH \rightarrow NaB(OCH_3)_4$;[25] this pattern may be influenced by disproportionation. The products of reduction will depend on the ratio of the various borohydride species present and their relative rates of reaction. Increase in the methanol content will yield more of the larger, more reactive trimethoxyborohydride (the participation of the tropoxy species in the reaction must play a less important role than in the case of $LiAlH_4$ reductions). The use of borohydride in ethanol might be expected to give an even larger ethoxyborohydride reducing species, but the contraindication of the results is easily explained by the slower rate of reaction between $NaBH_4$ and ethanol[31] and therefore the greater participation of the smaller BH_4^- species. This trend is further indicated in the case of *n*-butanol (Table 1, nos. 13, 14 and 15). The similarity of the isomeric ratios obtained using borohydride in water, tetrahydrofuran and *iso*propanol already noted is not unexpected since Brown *et al.*[30,31] have shown that $NaBH_4$ reacts with lower straight chain but not branched chain alcohols such as *iso*propanol and *t*-butanol.

Sodium trimethoxyborohydride in methanol might be expected to give isomeric ratios similar to those of borohydride in methanol; the discrepancy in the results (Table 1, nos. 13 and 22) is explicable in terms of the different contributions of two reactions, one the irreversible reaction of the borohydride with methanol, the other the reversible disproportionation of methoxyborohydrides as follows:

$$2\,NaBH(OCH_3)_3 \rightleftharpoons NaBH_2(OCH_3)_2 + NaB(OCH_3)_4.$$

The different results obtained using $NaBH(OCH_3)_3$ in methanol and in water indicates the increased contribution of large species in the former solvent, methanol reacting with the BH_4^- produced by disproportionation to give the larger substituted borohydrides (Table 1, nos. 20 and 22).

The reducing capacity of the borohydride ion is markedly affected by the metal ion present,[32] e.g. $NaBH_4$ reduces an ester slowly but $LiBH_4$ rapidly. Hardy and Wicker[13] found that KBH_4 in aqueous ethanol gave 41 per cent but $NaBH_4$ in aqueous methanol gave 61 per cent of the more stable isomer upon reduction of 2-methyl*cyclo*hexanone. However, changes in solvent composition rather than the cation component may have effected this result. Reduction of tropinone with $NaBH_4$ and KBH_4 in water gave results similar to those obtained using $LiBH_4$ in tetrahydrofuran (Table 1, nos. 6, 17 and 19); non-participation of the cation in the course of the reaction is therefore indicated.

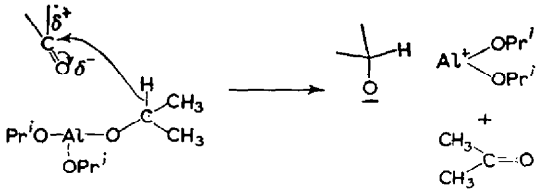
In order to establish whether nascent hydrogen plays a significant part in the reduction, an inverse addition to the ketone of a solution of sodium borohydride in water, in which visible evolution of hydrogen had ceased, was carried out, this gave an isomeric mixture similar to that obtained on direct addition (Table 1, nos. 7 and 9).

Aluminium iso*propoxide in* iso*propanol.* Cyclic intermediates in aluminium alkoxide reductions have been postulated.[33–36] Woodward[33] considered the hydride

[31] H. C. Brown, E. J. Mead and B. C. Subba Rao, *J. Amer. Chem. Soc.* **77**, 6209 (1955).
[32] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **78**, 2582 (1956).
[33] R. B. Woodward, N. C. Wendler and F. J. Brutschy, *J. Amer. Chem. Soc.* **67**, 1425 (1945).
[34] W. von E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.* **75**, 393 (1953).
[35] L. M. Jackman and J. A. Mills, *Nature, Lond.* **164**, 789 (1949).
[36] L. M. Jackman and A. K. Macbeth, *J. Chem. Soc.* 3252 (1952).

attack on the carbon of the carbonyl group to be the initiating and rate controlling step whereas Jackman *et al.*[35,36] considered an initial complexing of aluminium to the carbonyl oxygen followed by the rate controlling hydride attack on the carbonyl carbon.

Since equilibration involving Na and *n*-pentanol and $Al(OPr^{iso})_3$ gave comparable results, and reduction using the latter gave a much higher proportion of tropine than occurs in the equilibrated product, the following reaction in which the bulk effect of the reagent is in evidence in the kinetic control is indicated.



Co-ordination of the lone pair of the tropane nitrogen with aluminium may also facilitate approach from side "a" (see I) and so increase the production of the tropine isomer,

Sodium and alcohol. Recently Hardy and Wicker[13] have questioned whether reduction with sodium in alcohol always leads to production of the equilibrium mixture and have emphasised the importance of temperature in this reaction. Reduction of tropinone using Na in ethanol/toluene or in *iso*butanol/toluene under differing conditions of temperature gave results which were identical with those obtained on equilibration (Table 1, nos. 25, 26, 27 and 28, cf. 35 and 36).

EXPERIMENTAL

Materials. Distillation of commercial tropinone gave a pure sample which softened at 38° and melted at 41–43°. (Found: equiv. 140·8; Calc. for $C_8H_{13}ON$: 139·1) (Willstatter[37] quotes m.p 42°). Commercially available tropine had m.p. 42–49° (Found: equiv. 142; Calc. for $C_8H_{15}ON$: 141) and this was shown by infra-red analysis to contain 94 per cent. tropine and 6 per cent. ψ-tropine (tropinone was absent). Recrystallisation of the commercial tropine from benzene gave a sample m.p. 64° (Orechoff and Konowalowa[38] quote m.p. 63–64°) and this was used where necessary. Pseudotropine m.p. 109–110° was obtained by reduction of tropinone according to the method of Nickon and Fieser[41] (Willstatter *et al.*[37] quote m.p. 108°).

General. Organic layers, before evaporation to give the reduction product, were dried over anhydrous sodium sulphate. The reduction product was stored in a vacuum desiccator for at least 48 hr before assay. Equivalent weights were determined by titration with 0·02 N perchloric acid in glacial acetic acid with Oracet Blue B as indicator.[39] The percentage of total base (calculated as amino-alcohol equivalent weight 141·1) was calculated from the found equivalent weight.

Reduction with lithium aluminium hydride

(i) *Ether as solvent.* A solution of tropinone (5·0 g) in ether (20 cc) was added dropwise over a period of 0·5 hr to a suspension of $LiAlH_4$ (0·70 g) in ether (100 cc) and the mixture refluxed for 5 hr. After cooling, the mixture was decomposed with damp ether, and the ether solution separated. The inorganic residue was washed with ether, then refluxed with absolute alcohol, the combined organic layers filtered and evaporated to yield 4·93 g of a reduction product (2). In a similar reduction which was decomposed and extracted immediately after the addition of ketone, 4·52 g of a reduction product

[37] R. Willstatter, *Ber. Dtsch. Chem. Ges.* **29**, 936 (1896).
[38] A. Orechoff and R. Konowalowa, *Ber. Dtsch. Chem. Ges.* **67**, 1153 (1934).
[39] A. H. Beckett and E. H. Tinley, *Titration in Non-Aqueous Solvents* (2nd Ed.). British Drug Houses, Poole.

(1) was obtained. Tropinone (2·00 g) was reduced with $LiAlH_4$ (2·18 g) in ether (100 cc) refluxing for 3 hr, yielding 1·80 g reduction product (3). Reduction of tropinone (2·00 g) with an assayed solution of $LiAlH_4$ in ether (35·5 cc containing 0·0039 g $LiAlH_4$ in 1 ml)[40] yielded 1·80 g reduction product (4).

(ii) *Tetrahydrofuran as solvent.* The first reduction was repeated using tropinone (2·00 g) and lithium aluminium hydride (0·28 g) in tetrahydrofuran (100 cc) to give 1·96 g of reduction product (5).

Reduction with sodium borohydride

(i) *Water as solvent.* Sodium borohydride (0·40 g) was added to a solution of tropinone (5·00 g) in water (50 cc) when immediate effervescence occurred. The solution was allowed to stand for 24 hr at 20°, and was then extracted with chloroform (10 × 50 cc) which on evaporation gave 4·60 g of reduction product (7). The reduction was repeated (a) at 20° for 2 hr and (b) by refluxing for 48 hr when 4·79 g and 4·20 g respectively of reduction products were obtained (6 and 8). In a reverse addition, a solution of sodium borohydride (0·20 g) in 10 per cent aqueous sodium hydroxide solution (25 cc) was allowed to stand until all effervescence had ceased. A solution of tropinone (2·00 g) in water (25 cc) was added and after standing the solution at 20° for 2 hr it was extracted with chloroform, which on evaporation gave 1·81 g of reduction product (9).

(ii) *Aqueous methanol as solvent.* Sodium borohydride (0·80 g) was added to a solution of tropinone (2·00 g) in 25 per cent aqueous methanol (50 cc) when immediate effervescence occurred. After standing the solution at 20° for 6 hr the bulk of the solvent was evaporated, water (10 cc) added and the mixture extracted with chloroform, which on evaporation gave 1·84 g of reduction product (10). The reduction was repeated by refluxing for 6 hr using as solvent (a) 95 per cent aqueous methanol and (b) absolute methanol when 1·87 g and 1·95 g respectively of reduction products (12 and 13) were obtained. Tropinone was reduced by a modification of the method of Dauben *et al.*[11] A solution of sodium borohydride (0·66 g) in a mixture of 1 part water and 5 parts methanol (12 cc) was added to a solution of tropinone (2·50 g) in methanol (5 cc). After standing the solution at 20° for 16 hr the bulk of the solvent was removed under reduced pressure, water (10 cc) added and the mixture extracted with chloroform, which on evaporation gave 2·39 g of reduction product (11).

(iii) *Alcohols as solvent.* The reduction using absolute methanol was repeated using (a) absolute ethanol, (b) *n*-butanol and (c) *iso*propanol (2 hr reflux) as solvents when 1·89 g, 1·99 g and 1·97 g, respectively of reduction products 14, 15 and 16 were obtained.

Reduction with potassium borohydride

(i) *Water as solvent.* Potassium borohydride (0·26 g) was added to a solution of tropinone (2·00 g) in water (50 cc) when immediate effervescence occurred. After standing the solution for 24 hr at 20° it was extracted with chloroform, which on evaporation gave 1·90 g of reduction product (17).

(ii) *Methanol as solvent.* The reduction using sodium borohydride in methanol was repeated using potassium borohydride (1·17 g) when 1·87 g of reduction product was obtained (18).

Reduction with lithium borohydride

(i) *Tetrahydrofuran as solvent.* A solution of tropinone (2·00 g) in tetrahydrofuran (50 cc) was added dropwise during 0·25 hr to a stirred suspension of lithium borohydride (0·16 g) in tetrahydrofuran (50 cc) and the mixture refluxed for 5 hr. Water (10 cc) was added and the tetrahydrofuran separated. The aqueous layer was extracted with chloroform, the combined organic layer evaporated, the residue dissolved in dry ether, which after filtering and evaporation gave 1·90 g of reduction product (19).

Reduction with sodium trimethoxyborohydride

(i) *Water as solvent.* Sodium trimethoxyborohydride (0·9 g) was added to a solution of tropinone (2·00 g) in water (50 cc) and the mixture allowed to stand at 20° for 2 hr after which it was extracted with chloroform, which on evaporation gave 1·94 g of reduction product (20). In a similar experiment the mixture was refluxed for 48 hr yielding 1·99 g reduction product (21).

(ii) *Methanol as solvent.* Sodium trimethoxyborohydride (2·00 g) was added to a solution of tropinone (2·00 g) in methanol (50 cc) and the mixture refluxed for 6 hr. The bulk of the solvent was

[40] H. Felkin, *Bull. Soc. Chim. Fr.* 347 (1951).
[41] A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.* 74, 5566 (1952)

removed under reduced pressure, and water (10 cc) added. Extraction of the aqueous phase with chloroform gave on evaporation 1·82 g of reduction produce (22).

Reduction with aluminium iso*propoxide*

Tropinone (5·00 g) was added to a solution of aluminium *iso*propoxide (14·0 g) in absolute *iso*propanol (100 cc) and the solution heated in a water bath at 96° for 2·5 hr. The bulk of the solvent was removed under reduced pressure, and the residue acidified with acetic acid. On making alkaline with concentrated ammonium hydroxide solution, extraction with chloroform gave 4·62 g of reduction product (23). The reduction was repeated using tropinone (2·50 g), aluminium *iso*propoxide (7·0 g) and *iso*propanol (50 cc) and heating for 1·5 hr (when reduction was shown to be complete). The complex was decomposed with hydrochloric acid, made alkaline with sodium hydroxide solution, extracted with chloroform which on evaporation gave 2·39 g of reduction product (24).

Reduction with sodium–alcohol

A solution of tropinone (20·0 g) in a mixture of toluene (20 cc) and absolute ethanol (16 cc) was added over a period of 0·3 hr to sodium (6·5 g) in toluene (50 cc). The solution was refluxed for 3 hr, cooled, water (30 cc) added and the aqueous layer separated and extracted with toluene. A red oil was separated form the combined toluene layer and discarded, and the toluene evaporated to give 19·4 g of a reduction product (25). In a similar reduction using *iso*butanol in place of ethanol, 19·1 g of a reduction product (26) was obtained.

In a low temperature reduction, tropinone (2·06 g) in a mixture of toluene (20 cc) and *iso*butanol (3 cc) was added with stirring to an ice-cooled suspension of sodium (0·65 g) in toluene (20 cc) over 1 hr. The solution was stirred overnight, water (10 cc) added and extracted as above to give 1·83 g of a reduction product (27). In a similar reduction tropinone (2·02 g) yielded 1·80 g reduction product (28).

Equilibration of tropines

(i) *Sodium*/n-*pentanol.* The following general procedure was adopted. A solution of the alcohol (2 g) in *n*-pentanol (20 cc) was added to sodium *n*-pentoxide prepared from sodium (4 g) and *n*-pentanol (20 cc) and the mixture refluxed. After cooling and decomposing with water, dilute hydrochloric acid was added and the aqueous layer separated. This was made alkaline with dilute sodium hydroxide solution and extracted with chloroform, which on evaporation gave the equilibrium alcohol mixture (34–36).

(ii) *Aluminium* iso*propoxide.* The following general procedure was adopted. The alcohol (1·5 g) was added to a solution of aluminium *iso*propoxide (2·16 g) in *iso*-propanol (50 cc), acetone (0·5 cc) added, and the mixture refluxed. On completion of the reaction, acetic acid was added, the mixture made alkaline with concentrated ammonium hydroxide solution and extracted with chloroform, which on evaporation gave the equilibrium alcohol mixture (29–33).

(iii) *Sodium* iso*butoxide.* A solution of tropine (1 g) in a mixture of *iso*butanol (1·5 cc) and toluene (10 cc) was added, with stirring, to an ice-cooled suspension of sodium (0·33 g) in toluene (10 cc) over 1 hr. The solution was stirred overnight and water (5 cc) added, and the aqueous layer separated and extracted with chloroform. The combined organic layers were evaporated to give 0·91 g equilibrium alcohol mixture (37).