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Counterion Effect on Stereochemistry of Reduction of Cycloalkanones by Alkali Metals in Ammonia

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Abstract: An explanation for the observed stereochemistry of reduction of cycloalkanones with Li/NH_3 and K/NH_3 is given herein. The counterion effect wherein addition of excess KBr to Li/NH_3 results in epimer ratios closer to K/NH_3 has been confirmed in enough cases to enable the assumption to be made that the stereochemistry is dependent on the counterion present. The recently established e^-, e^-, H^+, H^+, pathway for such reductions is the basis for our explanation wherein the direction of ketyl radical anion pyramidalisation plays a crucial part. The one formed by addition of an electron to a bicyclo [2,2,1] heptan-2-one is assumed to have an **endo** C-O bond while the one produced from cyclohexanone is equatorially directed. It is postulated that the addition of the second electron gives initially two dianions in unequal amounts, the major one having the same configuration as its precursor. Association with two Li^+ ensures that these dianions are not interconverted and hence **endo** alcohols are the major products in Li/NH_3 reduction of the above bicyclic ketones and equatorial alcohols are the major products from cyclohexanones. When K^+ counterions are present interconversion via a dianion triplet is postulated as being fast enough so that the Curtin Hammett principle applies and the stereochemistry is determined only by the relative energies of transition states for C-protonation by a proton from the ketone. Epimer ratios obtained by us and others are accounted for.

INTRODUCTION

Reversal in epimer ratios in going from Li/NH_3 to K/NH_3 reduction of some, but not all, cyclic ketones has been a fascinating observation which has so far defied any explanation. The most significant early finding[2] was that in such a case presence of excess KBr in Li/NH_3 reduction gave an epimer ratio close to that obtained with K/NH_3. Presence of excess LiBr in K/NH_3 reduction gave a ratio close to that obtained with Li/NH_3. The clear indication was that the stereochemistry of reduction is governed by the nature of the counterion and not the metal. There was no fixed proven mechanism available to the earlier workers to provide an acceptable explanation[3]. This is no longer the case. A dianion mechanism has been established[4]. Using this we have offered explanations herein for practically all pertinent observations relating to Li/NH_3 and K/NH_3 reduction of a variety of substrates studied by our group, as well as taken from the literature.

RESULTS AND DISCUSSION

The specific observation that forms the basis of the present work is that of Murphy and Sullivan[2] using (+) camphor, **1**, as substrate. **Table 1** summarises their findings.

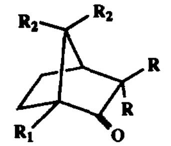
Table 1 Borneol, **5** and Isoborneol, **6**, Obtained in Reduction of (+) Camphor, **1**[2] in NH_3

Metal	Salt	Metal:Salt	Yield of alcohol	5:6	Pinacol
Li	--	--	25%	80:20	70%
Li	LiBr	1:5	25%	80:20	75%
K	LiBr	1:5	40%	76:24	60%
K	LiBr	1:1	60%	66:34	40%
Li	KBr	1:1	60%	67:33	40%
Li	KBr	1:5	70%	53:47	30%
K	—	--	95%	42:58	0%

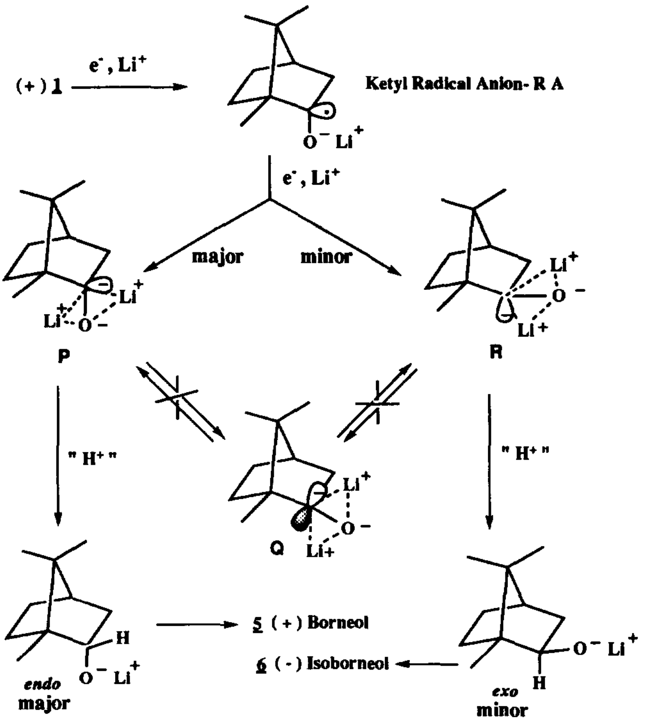
Before attempting an explanation it is desirable to refer briefly to the evidence supporting the dianion mechanism, i.e., the **e^-, e^-, H^+, H^+** pathway. The study by Dewald[5] of the kinetics of Na/NH_3 reduction of 2,2,4,4-tetramethylpentan-3-one (TMP) established that the rate determining step is the addition of an electron to the ketyl radical anion ion paired with Na^+. Protonation occurs subsequent to 1,2 dianion formation. Because TMP is a non-enolisable ketone, protonation is by NH_3. Coexistence of the starting ketone with the radical anion and dianion, permits the NH_2^- formed, to add to the carbonyl and thus effectively "trap" the ketone till work-up. The overall result is a 1:1 reduction:recovery. This work, in its totality, effectively removes all objections[6,7] to our earlier finding that an enolisable ketone capable of cyclising at the radical anion stage undergoes reduction to a secondary alcohol via a dianion with Na/NH_3[8,3]. Subsequent to its formation, the 1,2 dianion abstracts a proton from α to the ketone giving a 1:1 ratio for reduction:recovery. As stated in the original paper[8] the demonstration of the dependency of the ratio of reduction to cyclisation on [Na] alone established for compound **7** **(Chart 1)** and its analogues, eliminates all other mechanisms including the mechanism of reduction proposed recently by Huffman[9].

To establish that the validity of the relationship is not limited to Na/NH_3 alone a comparable study was undertaken for Li/NH_3. Details given in the Experimental Section confirm the validity for the latter.

Assuming on the basis of the data in **Table 1** that the stereochemistry is dependent on the counterion present rather than on the metal used, we propose to account for the results with Li^+ and K^+. These represent extreme cases with Na^+ lying between. We shall do so on the basis of the **e^-,e^-,H^+**, mechanism leading to the two epimeric alkoxides which protonate on workup to give the alcohols. Accepting the above pathway forces the conclusion that it is a proton and not hydrogen atom which becomes attached to carbon. In the case of nonenolisable ketones it is NH_3 which provides the proton. With enolisable ketones the primary source of the proton is the "acidic" hydrogen α to the ketone group. Two important and exhaustive studies by Rautenstrauch[10,11] using deuterated substrates have established this. Before going into the details it is desirable to look into the reason for the preference over NH_3. Of the two proton sources, NH_3 is a **"harder"** acid. The base in question is $R_2\overset{-}{C}—\overset{-}{O}$ dianion. This, as well as the corresponding hydroxy carbanion, can definitely be classified as **"soft"** bases. The di-potassium salt of the dianion[12] is expected to be the **"softest"** base in the series preferring to protonate at carbon by reaction with the "**softest**" acid available. Rautenstrauch found that trideuterated alcohols with a deuterium attached to the carbinol carbon are the major products in Li/NH_3, Na/NH_3 and K/NH_3 reduction of 2,2-dimethylcyclohexanone-6-d_2[10] and (+) camphor-d_2, **2**[11]. With the latter substrate both borneol, **5**, and isoborneol, **6**, are found to be substantially trideuterated. The reported extent of trideuteration of the two alcohols is between 58% and 91%. The hydrogen at the carbinol carbon can come to some extent from monodeuterated camphor produced under the reaction conditions. Making some allowance for a deuterium isotope effect the extent of protonation by NH_3 at carbon in the alkali metal/NH_3 reduction of unlabelled camphor, can be 20% at the most, probably less. Convinced that protonation by ammonia cannot play a significant role in determining the ratio of endo:exo alcohols produced we turn to our proposal dealing with the stereochemistry of reduction of (+) camphor, **1**, with Li/NH_3. A pictorial representation is given in **Scheme 1**.



1	CAMPHOR	R=H, R_1=R_2=CH_3
2	CAMPHOR-d_2	R=D, R_1=R_2=CH_3
3	NORCAMPHOR	R=R_1=R_2=H
4	FENCHONE	R=R_1=CH_3, R_2=H



Scheme 1

The most important feature of the proposal is the structure of the ketyl radical anion formed by adding an electron to the ketone and then associating with the available counterion. This species is regarded as being partially pyramidalised with the C-O bond **endo**. Our preference for such a configuration is a result of several considerations already dealt with in detail in the Tetrahedron Report Number R212[3]. Addition of another electron and Li+ to the ketyl radical anion is then expected to give the two epimeric dianions in unequal amounts the major one having a configuration in which the C-O bond is **endo**. This is **P** in **Scheme 1**, the other being **R**. The two Li^+ could have been shown as being localised at the anionic centres but in view of the enhanced stability associated with a "dicarbanion ion triplet" by Streitweiser[13], we have given a crude representation which takes into account a leaning to such association but retaining **sp**^{3} hybridised carbanions. Interconversion between these requires passage through the species **Q** having a **sp**^{2} hybridised carbanion. Our contention is that such interconversion, requiring loosening of the almost covalent $-O^-Li^+$ bonds is too slow to compete with protonation at carbon (with retention of configuration) of both **P** and **R**[14]. Ratio of borneol to isoborneol produced via the corresponding alkoxides is then expected to be the same as the ratio of **P** to **R** irrespective of whether the proton donor is the ketone or ammonia. In the case of K/NH_3 reduction in the presence of excess LiBr, the dianions associated with two Li^+ counterions, namely **P** and **R** are the main species with **P** being the major dianion initially produced whether the radical anion precursor is associated with Li^+ or K^+ since the pyramidalisation proposed for the ketyl radical anion (having an **endo** C-O bond) in **Scheme 1** is equally valid for K^+. **Table 1** indicates that the overall result when only K^+ is present is quite different.

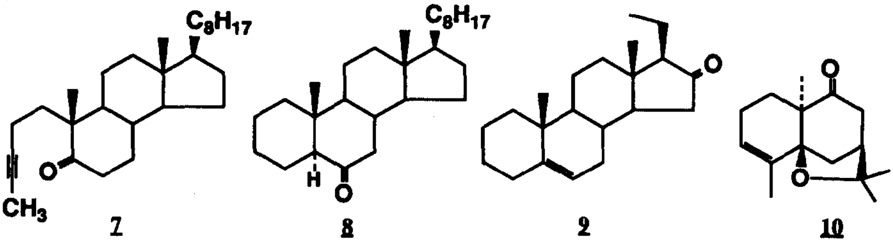
Let us now turn to the latter system, i.e., reduction of (+) camphor with K/NH_3. As before the two dianions are initially produced in different amounts. Amount of **P** (with two K^+ in place of two Li^+) would be much more than the amount of **R** (with two K^+ in place of two Li^+). But in this case we propose that interconversion via the analogue of **Q** having K^+ in place of Li^+ is facile. To explain the observed stereochemistry we postulate that the interconversion is so much faster than protonation at carbon of the dianion that the Curtin Hammett principle[15] applies. Thus the ratio of epimers is governed neither by the amounts of the two dianions initially produced, nor by the relative amounts of dianions produced by equilibration, but only by the relative energies of the transition states for C-protonation. Assuming that protonation of the carbanions occurs with retention of configuration the results obtained with (+) camphor require that the least energy transition state is one in which the proton delivery is by a molecule of (+) camphor itself[16] to that particular dianion which has a C-O **exo** and the lone pair of electrons at carbon **endo** viz: **R** of **Scheme 1** with K^+ in place of Li^+. The **exo:endo** ratio of 58:42 indicates that the transition state for proton delivery by (+) camphor to the **exo** directed lone pair of the other dianion is only slightly higher in energy. The primary factor which determines the stereochemistry in K/NH_3 is the ease of approach of the bulky molecule of ketone in such a manner that a proton α to the ketone is delivered to the dianion at carbon.

An attractive proving ground for this was the steroid molecule in that ease of approach from the α face can generally be taken for granted. Cholestan-6-one, 8, is a typical steroidal 6-membered ketone which gives the equatorial cholestan-6α-ol on reduction with Li/NH_3. Since, in all except the most hindered cases, the ketyl radical anion derived from cyclohexanones are pyramidalised with the C-O bond equatorial[3] it will form the corresponding dianion and finally the equatorial alcohol as per the link between the direction of pyramidalisation of the ketyl radical anion and the structure of the major alcohol in Li/NH_3 reduction proposed in **Scheme 1**. The same substrate in K/NH_3 reduction should yield cholestan-6β-ol which is an axial alcohol. This was predicted on the grounds that the transition state of lowest energy would be one in which the dianion having a C-O bond axial and the lone pair of electrons on carbon directed equatorial, i.e., in the α direction, to receive a hydrogen located α to the ketone, as a proton, in a bimolecular reaction with the ketone approaching from the α face. For identical reasons cholestan-2-one was expected to be reduced by K/NH_3 to the axial cholestan-2β-ol. It does. Compound **9** (**Chart 1**) is a 5-membered ketone in which the $C^{\bullet}$-O^{-} bond is directed α[17]. The major product with Li/NH_3 is hence the 16α-ol. But in K/NH_3 the governing factor being ease of approach from the α face, the formation of 16β-ol is favoured[18]. The exact ratios are given in **Table 2**. In this Table a variety of data is collected wherein the stereochemistry of reduction with both Li/NH_3 and K/NH_3 has been determined. The Na/NH_3 result is available in most cases while the effect of the presence of excess KBr in Li/NH_3 is given in some. Our endeavour is to cover all these findings.

Table 2 Epimer ratios in Li, Na, K and Li:KBr (1:5)/NH_3 reduction of cycloalkanones

Compound	Alcohols	Li	Na	K	Li + KBr
(+) camphor[2] **1**	5 endo 6 exo	80 20	60 40	42 58	53 47
(+) camphor-d$_2$[11] **2**	5-d$_3$ 6-d$_3$	78 22	53 47	34 66	---
norcamphor[19] **3**	endo exo	70 30	70 30	80 20	---
4-methyl-4,5-secocholest-3-yn-5-one **7**	5β-ol	100	100	100	---
cholestan-6-one **8**	6α-ol 6β-ol	91 9	---	36 64	45 55
pregn-5-en-16-one **9**	16α-ol 16β-ol	57 43	43 57	24 76	40 60
(±) camphor[20]	endo exo	80 20	81 19	82 18	---
9-oxo-α-agrofuran[21] **10**	9α-ol 9β-ol	59 41	25 75	17 83	---
fenchone[19] **4**	endo exo	98 2	98.5 1.5	99 1	---

We wish to emphasize that with steroidal ketones the major product expected in K/NH_3 reduction is the alcohol having the β configuration. It does not have to be axial. The 5βol obtained as the sole secondary alcohol in K/NH$_3$ reduction of the secosteroid 7, illustrates this. Li/NH$_3$ reduction, on the other hand favours the formation of the equatorial alcohol which happens to be 5β.



7 8 9 10

Chart 1

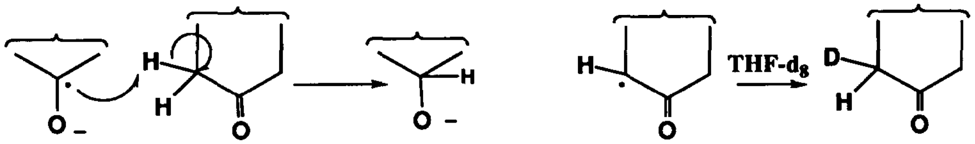
Norcamphor, **3**, has the distinction of giving mainly the thermodynamically less stable alcohol on reduction with Na/EtOH[3]. The **endo** alcohol is obtained. The **exo:endo** ratio at equilibrium is found[19] to be 75:25. Norcamphor (see **Scheme 1**) is an unsubstituted member of the bicyclo [2,2,1] heptan-2-one series of compounds. We have previously pointed out that the corresponding ketyl radical anion in this series is pyramidalised with the C-O bond **endo** as seen in **Scheme 1** for camphor. That the **endo** alcohol is the predominant product in Li/.NH$_3$ reduction of **3** is to be expected. Formation of the same product in K/NH$_3$ reduction is ascribed to lower steric hindrance to approach from the **exo** face compared to the **endo** face in the absence of methyls on C-7.

The remarkable result[20] wherein (±) camphor gives mainly (±) borneol with K/NH$_3$ or Li/NH$_3$ whereas (+) camphor gives (-) isoborneol with K/NH$_3$ and (+) borneol with Li/NH$_3$ can be satisfactorily accounted for using the dianion mechanism in which the rate determining step is dianion formation. For simplicity let us consider the fate of the dianions from (+) camphor for both substrates. Starting with (+) camphor we have the situation already discussed with reference to **Scheme 1**. In K/NH$_3$ reduction we have two dianions which are interconverting. Each is seeking a proton from (+) camphor. Of the two possible transition states for **exo** proton transfer[16] the lower energy one leads to (-) isoborneol. With (±) camphor as substrate for K/NH$_3$ reduction, we will again pursue the fate of the two dianions from (+) camphor. Besides the above two transition states two more are available since (-) camphor is present to donate its protons. The lowest energy transition state[22] among the four gives (+) borneol. Actually (±) borneol is produced because a corresponding reaction of (-) camphor generates an equal amount of (-) borneol. In Li/NH$_3$ reduction the proton delivery step has no control over the stereochemistry of reduction and so the same result is obtained with (±) camphor and (+) camphor.

9-Oxo-α-agrofuran[21] **10** is a special case in that steric hindrance to approach from β position to the dianion having the C-O bond equatorial is so high that another molecule of the ketone 10 cannot be expected to approach from that side. Hence the 9α-ol must arise by protonation with NH$_3$ in the reaction with K/NH$_3$. This comprises only 17% of the alcohols produced. The remaining 83% involves the other dianion having an axial C-O bond. Proton delivery at the equatorial position obviously has the lower energy transition state. As usual the "**soft**" base is expected to have a lower energy transition state for abstracting an hydrogen from α to the ketone molecule than for abstracting a proton from NH$_3$. A pointer to the accuracy of this is the finding [21] that 9-oxo-α-agrofuran-8-d_2 (containing 25% d_1) on reduction with Na/NH_3/t-BuOH gave the 9β-ol having 43% deuterium in the 9α position while the 9α-ol formed has no deuterium at the carbinol position (C-9). The equatorial alcohol is the major product in reduction of **10** with Li/NH_3 consistent with **Scheme 1** as applied to a cyclohexanone.

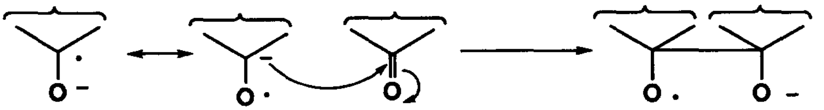
In the case of the non-enolisable ketone, fenchone, **4**, the formation of **endo** alcohol as the major product in Na/EtOH reduction has been assigned to the typical pyramidalisation of the ketyl radical anion[3]. The Li/NH_3 reduction follows suit[19]. For K/NH_3 reduction it appears that in spite of the small size of the proton delivering agent, namely ammonia, the energy of the transition state resulting in the **endo** product is less than the energy of the transition state wherein the pyramidalised dianion, with the C-O bond **exo**, abstracts a proton from NH_3. A contributing factor for raising the energy may be greater steric repulsion. An alternative explanation is that steric factors influence Q (with K^+ in place of Li^+), preventing interconversion of dianions.

Before leaving the subject of alkali metal/NH_3 reduction of cyclic ketones it is desirable that we examine the data Huffman has used for arriving at an alternative mechanism for reduction of enolisable ketones[9]. In alkali metal/NH_3 reduction of (+) camphor in the presence of THF-d_8, the recovered camphor was found to be partially deuterated. This led him to propose the following:



We have pointed out that our work with enolisable ketones rules out this possibility as ratio of reduction to cyclisation in alkali metal reduction of **7** is independent of ketone concentration. So the generation of the α keto radical must be by a process other than the one indicated above. In his study of Li/NH_3/THF reaction of (+) camphor Huffman himself has provided[9] proof that the pinacolisation which accompanies reduction, involves the intermediate **F** given below which has an alkoxy radical group. Such a group is efficient at hydrogen atom abstraction and hence it is species **F** *and not the ketyl radical anion* which is responsible for the generation of the α keto radical. Consistent with this is the observation that in K/NH_3/THF-d_8 reduction, wherein pinacol formation is absent, the camphor obtained is virtually undeuterated. The question of how the alkoxy radical is generated is of considerable interest and will be dealt with briefly here.

We recently made a rare find relating to enantioselectivity in pinacolisation of camphor[23]. We proposed in our paper that the **endo, exo** pinacol produced at low concentration of Li arises as follows:



F

Subsequently Huffman reported work on pinacolisation[24] in which he agreed that the **endo, exo** pinacol resulted via intermediate **F** (having an alkoxy radical function) formed by attack of ketyl radical anion on ketone. In the same paper he proposed initial attack of the radical centre of a ketyl on an unreduced ketone molecule. This was quite distinct from our proposal wherein the species **F** is formed as a result of nucleophilic attack by the the ketyl radical anion as shown above. Fortunately Huffman's work provides the data for distinguishing between the two possibilities. The intermediate species **F** was found to give on the one hand the **endo, exo** pinacol but on the other an isomeric hydroxy ketone by ß cleavage of the alkoxy radical in **F**. An **exo** hydroxyl is retained in the hydroxy ketone. This establishes that the intermediate having part structure **F** has an **endo** alkoxy radical and an **exo** alkoxide anion.

Even on the basis of the limited assumption that the ketyl radical anion approaches camphor from the less hindered **endo** direction it follows that attack by it as a nucleophile will give the correct intermediate having an **exo** alkoxy anion. Attack as a radical will not.

Since the pyramidalised ketyl radical anion from camphor has an **endo** C-O bond the **exo** lobe involved in nucleophilic or radical attack would have produced the intermediate with an **endo** C-O$^{\bullet}$ and C-O^{-} respectively. Thus we see that **endo** approach is not the only criterion supporting nucleophilic addition[25].

The demonstration that the ketyl radical anion behaving as a nucleophile at carbon adds to a carbonyl group is important in that it demonstrates the versatility of the ketyl radical anion. In cyclisation by attack on a triple bond the ketyl radical anion attacks as a radical and not as a nucleophile. This has been established earlier by our group using compound **7**[26].

Finally we would like to draw attention to the finding that when camphor-d_2 was reduced with Li, Na or K/NH_3 in the presence of excess NH_4Cl, the **endo** alcohol was the major product and it had no deuterium at the carbinol carbon[11]. 9-Oxo-α-agrofuran showed a similar pattern in giving exclusively the 9α-ol on Li/Na/K in ammonia reduction in the presence of excess ethanol[21]. This is not a matter of thermodynamic control since norcamphor gives the less stable alcohol in alkali metal/NH_3 reduction in the presence of NH_4Cl[27]. These observations justify drawing attention to the fact that the alcohols formed under these conditions have the same configuration with respect to the C-O bond as the ketyl radical anion from which they are generated.

EXPERIMENTAL SECTION

General Methods: Infrared spectra were obtained with a Perkin Elmer Model 397 double-beam spectrophotometer. NMR spectra were recorded on Varian EM 360L spectrometer. Optical rotations were determined in $CHCl_3$ at room temperature with a Carl Zeiss Winkel spectropolarimeter. THF was purified for all purposes by being refluxed initially with sodium followed by another distillation from $C_{10}H_8Na$. Sodium benzoate was freshly dried at 110°C under vacuum for 3 hours before use. All reactions as well as column chromatography were followed by TLC using microslides.

Starting Materials: The following starting materials were prepared according to the literature. 4-Methyl-4, 5-secocholest-3-yn-5-one[26], **7**; cholestan-6-one[28], pregn-5-en-16-one[17], cholestan-2-one[29].

Reduction of 7 with Li/NH_3/THF: The technique developed and described in Ref. 8 was followed.

4-Methyl-4,5-secocholest-3-yn-5-one, **7**, after reaction with Li in NH_3 plus THF was quenched with sodium benzoate, workup followed by chromatography on silica gel gave starting material, followed by a mixture of (E) and (Z) 3-ethylidene-A-norcholestan-5β-ols. Finally, 4-methyl-4,5-secocholest-3yn-5β-ol[26] m.p. 78-80°C, $[\alpha]_D$+12° (c 0.10) was eluted.

A number of experiments with varying concentrations of Li and **7** were carried out. The result is given in the following Table.

			Time		Ratio		Redn.
Run	[7] M	[Li] M	m Min.	[Li]/[7]	Redn./Recovery	Redn./Cycl.	Cyclx [Li]
1	0.0052	0.0443	15	8.52	1.0	1.28	29.0
2	0.0067	0.0443	15	6.61	0.956	1.19	26.86
3	0.02	0.0443	10	2.215	0.986	1.18	26.63
4	0.02	0.177	10	8.85	0.984	5.59	31.60

This establishes that: $$\frac{\text{Rate of Reduction}}{\text{Rate of Cyclisation x [Li]}} = 29 \pm 3$$

Reduction of 7 with K/NH_3/THF: Following an identical procedure the same compounds were isolated, but ratio of reduction/recovery was 1.56. In the case of Li as well as Na it was close to 1 meaning that the enolate formed did not ketonise till work up. In the case of K, ketonisation was occuring and hence there was no point in attempting to establish any relationship.

Reduction of cholestan-6-one, 8, with alkali metal/NH_3: To anhydrous distilled NH_3 (40 ml) was added the alkali metal (3 mg. atom) and solution stirred for 1 minute in the special apparatus used in earlier work. Cholestan-6-one (300 mg; 0.78 mmol) in dry THF (10 ml) was injected into the blue solution. The reaction was quenched after 5 minutes by addition of sodium benzoate. Workup and chromatography on alumina gave recovered starting material, followed first by cholestan-6ß-ol[28] and then by cholestan-6-α-ol[30]. The ratio of the alcohols obtained using Li, K and Li + KBr in the ratio of 1:5 is given in **Table 2**.

Reduction of pregn-5-en-16-one, 9, with alkali metals in NH_3: Pregn-5-en-16-one17 gave by the same method pregn-5-en-16-ol[17] and pregn-5-en-16ß-ol[17]. The ratios of the two were determined for Li, Na, K and Li + KBr in the ratio of 1:5. they are given in **Table 2**.

Reduction of cholestan-2-one- with K/NH_3: To anhydrous distilled NH_3 was added K (100 mg., 2.5 mg. atom) and after stirring for one min. cholestan-2-one (250 mg., 0.65 mmol) in dry THF (10 ml). The reaction was stirred and quenched after 5 min. by addition of sodium benzoate. Workup and chromatography on alumina yielded starting material (118 mg) followed by cholestan-2β-01[31] (68 mg) and cholestan-2-α-ol[32] (46 mg).

All the alcohols reported above had constants identical with those in the literature. Their nmr spectra supported the structures.

ACKNOWLEDGEMENT

This paper is dedicated to Professor Sir Derek Barton on his 75th birthday. May he continue to operate at the Frontiers of Science.

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