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Disproportionation versus Dianion Intermediacy in Alkali Metal Reduction of Saturated and Unsaturated Ketones

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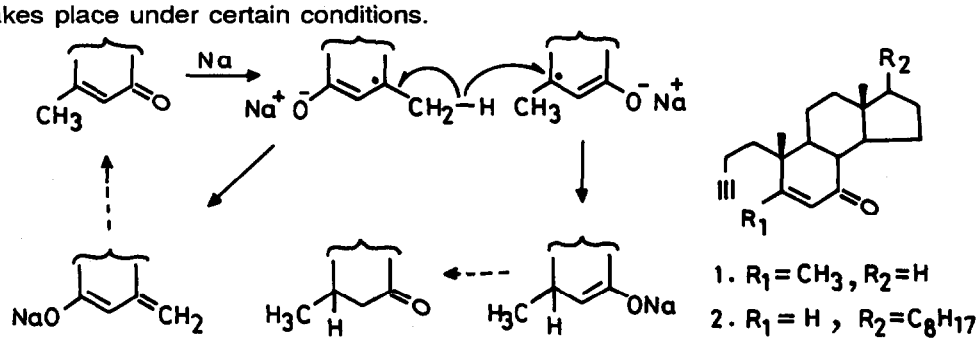
Abstract : Reduction of 5-methyl-4,5-secoandrost-3-yn-5-en-7-one, **1**, to 5 β- methyl-4,5-secoandrost-3-yn-7-one, **4**, is shown by **deuterium labelling** to proceed via **γ hydrogen transfer** when $C_{10}H_8Na$ is used whereas Na/NH_3 traps the intermediate radical anion by reduction to a **dianion.**

Disproportionation by hydrogen atom transfer from α to a radical to the semi-occupied orbital of another molecule is well known for alkyl radicals[2]. Whether radical anions, associated with alkali metal counter ions, derived from saturated and $\alpha\beta$ unsaturated ketones by reaction with alkali metals, undergo such a reaction is an important matter awaiting settlement[3]. Using **deuterium labelling** we have established that the disproportionation shown in **Scheme 1** takes place under certain conditions.

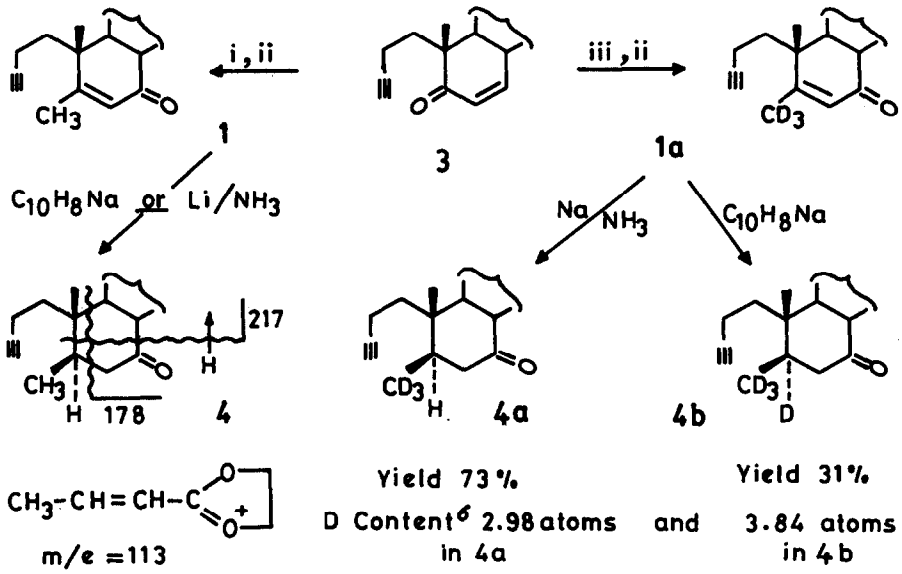


Scheme-1

The substrate chosen was 5-methyl-4,5-secoandrost-3-yn-5-en-7-one, **1**. The reagent of choice was $C_{10}H_8Na$/THF. This has the advantage of giving radical anions of adequate half life and in sufficient concentration to render the above bimolecular reaction feasible. Thus the corresponding cholestane derivative 4, 5-secocholest-3-yn-5-en-7-one, **2**, having no methyl at 5, gives with $C_{10}H_8Na$/THF, radical anion derived products[4] including combination. Absence of reduction ruled out hydrogen atom transfer. Its failure can be ascribed to inaccessibility of the hydrogen at C-8.

The preparation of **1** and its **trideuterated** analogue **1a** from **3**[5] is summarised in **Scheme 2** along with the results of their reactions with

$C_{10}H_8Na$/THF on the one hand and alkali metal/NH_3/THF on the other[8]. The stereochemistry assigned to the methyl at C-5 in **4** is based on the usual assumption that Li/NH_3 reduction of the enone will generate an equatorial methyl. The yield of 5β-methyl-4,5-secoandrost-3-yn-7-one, **4** with Li/NH_3 was 80% whereas with $C_{10}H_8Na$ it was 30%. Enone **1** recovered was 52%.



i) CH_3Li, Ether ii) Pyridinium chlorochromate, iii) CD_3Li, Ether[7]

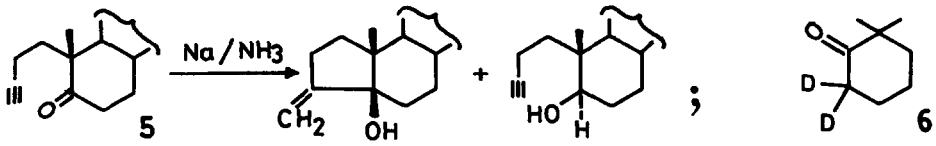
Scheme-2

Evidence confirming structure **4** includes IR, NMR[9] and Mass Spectra[10]. Origin of two of the fragments is depicted in **Scheme 2.** The ketal of **4** with ethylene glycol gives an intense base peak at m/e 113 which includes C-5 and the methyl and hydrogen attached to it. In the ketal derived from **4b** the intense base peak shifts to m/e 117 confirming the location of the four deuterium atoms. Possibility of deuterium being at C-6 or elsewhere is ruled out since m/e at 217 and 178 are seen in both **4a** and **4b** also. The molecular ion as well as the m/e of a number of significant fragments are seen in the mass spectra of **4a** and **4b** to be increased by three and four mass units respectively[11] relative to **4.** The tetradeuterated ketone **4b** obtained in 31% yield by the action of $C_{10}H_8Na$ on **1a** was accompanied by dideuterated **1** in 35% yield along with untouched **1a** in 8% yield. It follows that the disproportionation envisaged in **Scheme 1** is the major pathway to the reduction product.

The same batch of freshly prepared **1a** was simultaneously subjected to Na/NH_3 reduction[8b] and gave **4a.** The total absence of deuterium at C-5 provides strong evidence that a different mechanism is operative. In a critical "Report" on the subject[12] of alkali metal/ NH_3 reduction of enones and ketones it was pointed out that the preferred mechanism in both cases involved the "e^-, e^-, H^+, H^+" (with

one or more of e^- being replaced by an atom of alkali metal) path. The failure to observe disproportionation of the radical anion produced from **1a** by Na/NH_3 can be ascribed to rather rapid addition of the second electron by this stronger reducing agent. It should be recalled that House reduced 3,5,5-trimethylcyclohex-2-en-1-one with $Li/NH_3/(CH_3)_2CDOH$ but failed to incorporate deuterium[13] at C-3. The failure of the intermediate radical anion to abstract deuterium atom from an efficient donor can be linked with short half life of the radical anion because of rapid reduction to the dianion. A similar explanation has been given[12] to account for the failure to detect radical combination or cyclisation products in the Na/NH_3 reduction of the "desmethyl" compound **2** referred to above. Only product is 4, 5-secocholest-3-yn-7-one. Yield 96%.

The only objections to dianion formation from enones by Na/NH_3 are based on presumed non-availibility of adequate reduction potential[13] in the reducing system. These considerations have been rendered invalid by the recent finding that a saturated ketone which should require a much higher reduction potential[14] to yield a dianion is reduced by Na/NH_3 via a 1,2 dianion. The break-through has been provided by a timely and significant study by Dewald[15] of the kinetics of Na/NH_3 reduction of 2,2,4,4-tetramethylpentan-3-one. The rate determining step proved to be the addition of e^- to the ketyl radical anion (associated with Na^+) to give a dianion (associated with Na^+). Evidence for similar 1,2 dianion intermediacy in alkali metal/NH_3 reduction of enolisable ketones had previously been obtained by us[4]. Using 4,5-secocholest-3-yn-5-one, **5** and related compounds we found that the ratio of reduction to cyclisation shown below was directly proportional to the concentration of alkali metal[4].



Unlike Na/NH_3, $C_{10}H_8Na$ gave no reduction product on reaction with **5**.. Only cyclisation and recovery via enolate was observed[16]. This eliminates the possibility of the ratio being dependent on concentration of say Na^+ in place of Na as proposed by Rautenstrauch[14b]. The intermediate radical anion from **5** does not combine or disproportionate. These typical radical reactions are presumably not as fast in ketyl radical anions because of the influence of the adjacent negatively charged oxygen.

Another criticism levelled at the dianion mechanism is based on an erroneous presumption[14b]. It is true that for alkali metal/NH_3 reduction of 2,2-dimethylcyclohexanone-6-d_2 **6** we proposed that the corresponding dianion abstracts a deuteron from another molecule of **6**. We have not stated that the dianion survives in the presence of excess ethanol. On the contrary we have suggested that a hydroxy carbanion is formed (by protonation of dianion at $-O^-$ by EtOH) which abstracts a deuteron from α to the carbonyl group of another molecule of **6**[17].

The failure to observe an equivalent γ deuteron abstraction from **1a** by the dianion formed from another molecule of **1a** is because thermodynamics of first electron addition to **1a** ensures that no **1a** is available.

It remains to point out that the **Barton[18] dianion mechanism** for Li/NH_3 reduction of saturated and unsaturated ketones stands **resurrected.**

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5. This is prepared from androst-4-en-3-one which has been reported by Shapiro R.H. and Djerassi C. J.Am. Chem. Soc. 1964, 86, 2825. It was epoxidised, and after Eschenmoser fragmentation brominated and dehydrobrominated as described for the cholestane analogue by Pradhan S.K., Kadam S.R., Kolhe J.N., Radhakrishnan T.V., Sohani S.V., and Thaker V.B., J. Org. Chem. 1981, 46, 2622.
6. We are grateful to Dr. Pramanik of Schering Corporation, Bloomfield, NJ, USA for determining CI+/Isobutane mass spectra of **4, 4a** and **4b** and providing us with an accurate estimate of deuterium in **4a** and **4b.**
7. NMR grade CD_3OD was converted to CD_3I using red P and I_2. The purity of CD_3I was confirmed using nmr and then CD_3Li/ether was prepared.
8. a) To freshly prepared $C_{10}H_8Na$ (0.4N) in THF (6.2ml) was added **1** (284 mg) in THF (5 ml) at 30°C under N_2. Stirring continued for 10 min. then added CH_3OH.
   b) Li (16 mg) was added to anhydrous NH_3 at -33°C (20 ml) and after stirring for 2 min. was added **1** (240 mg) in THF (5 ml) under N_2. After additional 5 min. stirring quenched with sodium benzoate. (In Na/NH_3 reaction of **1a**, Na (36 mg) and **1a** (220 mg) were used.)
9. **4** had IR (Nujol) ν_m : 3300, 2100, 1705 cms^{-1} : ^1H NMR (CCl_4, Me_4Si) δ : 0.65 (s, 3H, methyl), 1.0 (s, 3H, methyl), and 0.9 (d, 3H, J=7 Hz. methyl at C-5) ^{13}C NMR ($CDCl_3$, Me_4Si) δ : 211.81, 84.19, 68.19, 49.63, 48.91, 46.93, 40.26, 39.35, 38.68, 37.59, 35.08, 26.14, 21.85, 20.47, 17.13, 15.76, 14.88, 11.37.
10. MS of **4** : m/e(%) 286(20), M^+; 271(14), 253(9), 243(6), 232(24), 217(28), 203(43), 190(17), 178(42), 163(28), 145(33), 135(100) and 121(50).
11. All underlined values in Ref.10 are found to be replaced by m/e three mass units higher in the MS of **4a** and four units higher in the MS of **4b.** The rest have same values in **4, 4a,** and **4b.**
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