ammonia was added a solution of 150 mg (0.5 mmol) of the ethylenic aldehyde **44** in 5 mL of THF. After 4 min, workup and chromatography on alumina with benzene as an eluent initially gave 42 mg of the starting material **44**. Later fractions gave 39 mg of pregn-5-en-16β-ol (**47**). It was crystallized from methanol: mp 97–99 °C; $[\alpha]_D$ –60° (*c* 0.1); IR (Nujol) 3430 (OH), 1030, 1005, 830 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.0 (3 H, s, C-19 methyl), 4.23 (1 H, m, C-16 H), 5.17 (1 H, m, C-6 H). Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.67; H, 11.59. Further fractions gave 52 mg of pregn-5-en-16α-ol (**46**). It was crystallized from chloroform/methanol: mp 174–176 °C; $[\alpha]_D$ –103.33° (*c* 0.1); IR (Nujol) 3300 (OH), 1340, 1060, 835 cm^{-1}; NMR ($CDCl_3$) δ 0.57 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 3.97 (1 H, m, C-16 H), 5.27 (1 H, m, C-6 H). Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.52; H, 11.44. The last fraction gave 7 mg of a product which was not characterized.

Action of Sodium/Liquid Ammonia on (*E*)-16-Methyl-16,17-secopregna-5,17(20)-dien-16-one (45). To a stirred solution of 55 mg (2.4 mmol) of sodium in 20 mL of anhydrous and redistilled ammonia was added 150 mg (0.48 mmol) of ethylenic ketone **45** in 5 mL of THF. After 4 min, workup and chromatography on alumina with benzene as eluent initially gave 45 mg of the starting material **45**. Later fractions gave 39 mg of 16α-methylpregn-5-en-16β-ol (**50**). It was crystallized from methanol: mp 99–101 °C; $[\alpha]_D$ –58.4° (*c* 0.1); IR (Nujol) 3400 (OH), 1340, 1070, 940, 895 cm^{-1}; NMR (CCl_4) δ 0.77 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 1.25 (3 H, s, C-16 methyl), 5.16 (1 H, m, C-6 H). Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.24; H, 11.38. The last fractions gave 55 mg of 16β-methylpregn-5-en-16α-ol (**49**). It was crystallized from methanol: mp 145–147 °C; $[\alpha]_D$ –77.43° (*c* 0.1); IR (Nujol) 3400 (OH), 1310, 1120, 920, 875 cm^{-1}; NMR (CCl_4) δ 0.57 (3 H, s, C-18 methyl), 0.97 (3 H, s, C-19 methyl), 1.2 (3 H, s, C-16 methyl), 5.16 (1 H, m, C-6 H). Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.50; H, 11.80. Compound **45** (150 mg, 0.48 mmol) was reacted with 165 mg (7.17 mmol) of Na in NH_3 for 15 min as above. The reaction gave 28 mg of starting material, 45 mg of **50**, and 65 mg of **49**. TLC showed complete absence of **39**.

Results of addition of *t*-BuOH and of replacement of Na by Li are given in Table II.

Relative Reactivities of 40 and 45. To a stirred solution of 97 mg of sodium in 40 mL of NH_3 was added a mixture of 200 mg each of **40** and **45** in 10 mL of THF. Workup after 1 min followed by column chromatography yielded 61 mg of **45**, 30 mg of **40**, and 275 mg of a mixture of more polar compounds, excluding **40** and **45**. Thus **40** appears to react twice as fast as **45**.

Acknowledgment. We are grateful to Nivedita Chemicals Pvt. Ltd. for generous gifts of 16-DPA and dry ice and to Cipla Pvt. Ltd. for meeting part of our cholesterol requirements. We thank Drs. D. N. Kirk and P. M. Scopes for the CD measurement as well as its interpretation. Our thanks are due to numerous well-wishers for helping us with NMR and mass spectra and C and H analysis, particularly at Ciba-Geigy, Schering Corp., and the Chemistry Department of Pune University. We are grateful for fellowships awarded by the University Grants Commission to T.V.R. and S.R.K. and by the Council of Scientific and Industrial Research to V.B.T., J.N.K., and S.V.S.

Registry No. 1a, 21489-86-1; **1b**, 58502-98-0; **1c**, 77081-48-2; **1d**, 58503-18-7; **1e**, 77081-49-3; **2a**, 21489-85-0; (*E*)-**2b**, 58503-11-0; (*E*)-**2b** β-epoxide, 58503-14-3; (*Z*)-**2b**, 58503-12-1; (*Z*)-**2b** β-epoxide, 58503-13-2; **2d**, 58503-19-8; **2e**, 77081-50-6; **3a**, 32232-84-1; **3b**, 32232-85-2; **4**, 77071-08-0; **5**, 77081-51-7; **6**, 77081-52-8; **7**, 77081-53-9; **8**, 77081-54-0; **9**, 77081-55-1; **10**, 77081-56-2; **11**, 77081-57-3; **12**, 77081-58-4; **13**, 77081-59-5; **14**, 77081-60-8; **15**, 77081-61-9; **16**, 77081-62-0; **17**, 77081-63-1; **18**, 77081-64-2; **19**, 77081-65-3; **20**, 77081-66-4; **20** tosyl hydrazone, 77081-67-5; **21**, 77081-68-6; **22**, 77081-69-7; **23**, 77081-70-0; **24**, 77081-71-1; **25**, 77081-72-2; **26**, 77081-73-3; **27**, 77071-10-4; **28**, 6996-36-7; **29**, 60069-43-4; **30**, 77081-74-4; **31**, 26538-48-7; **32**, 77081-75-5; **33**, 77081-76-6; **34**, 77081-77-7; **35**, 77097-77-9; **36**, 77081-78-8; **37**, 77081-79-9; **38**, 77081-80-2; **39** (isomer 1), 77111-00-3; **39** (isomer 2), 77111-01-4; **40**, 77081-81-3; **41**, 77081-82-4; **42**, 77081-83-5; **43**, 77081-84-6; **44**, 77097-02-0; **45**, 77081-85-7; **46**, 77081-86-8; **47**, 77081-87-9; **48**, 77081-88-0; **49**, 77081-89-1; **50**, 77081-90-4; 7α-methyl-4,5-secocholest-3-yn-5α-ol, 77081-91-5; 4,5-secocholest-3-en-5β-ol, 77071-09-1; 4-methyl-4,5-secocholest-3-yn-5β-ol, 58503-16-5; 4-deuterio-4,5-secocholest-3-yn-5α-ol, 77081-92-6; 4-deuterio-4,5-secocholest-3-yn-5β-ol, 77081-93-7; 4a,5-seco-*A*-homocholest-4(4a)-yn-5α-ol, 77081-94-8; 4a,5-seco-*A*-homocholest-4(4a)-yn-5β-ol, 77071-07-9; 5β-methyl-3-methylene-*A*-norcholestan-7-one, 77081-95-9; 5β-methyl-4,5-secocholest-3-yn-7-one, 77081-96-0; 3-methyl-*A*-norcholest-3(5)-ene, 6908-07-2.

Supplementary Material Available: Preparation and melting point, $[\alpha]_D$, IR, and NMR data for **10–13**, **19**, **21–25**, **29**, **30**, **32**, **35–37**, and **48** as well as C and H analysis of all except **22**, **24**, and **25**; unsuccessful attempts at conversion of **20** to **25**; details of naphthalene–sodium reaction on **10** and **13**; structure and stereochemistry determinations for **27**; alternative preparations of **33**, **34**, **42**, **43**, **46**, **47**, and **50** (8 pages). Ordering information is given on any current masthead page.

Mechanism of Reduction of Enolizable Saturated Ketones and α,β-Unsaturated Ketones by Sodium in Liquid Ammonia

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Received November 12, 1980

The ratios of reduction product to (reductive) cyclization product obtained from the reactions of 4-methyl-4,5-secocholest-3-yn-5-one (**1b**) and 4,5-secocholest-3-en-5-one (**4**) with Na/NH_3/THF were found to be directly proportional to the initial concentration of sodium/electrons taken in excess but independent of ketone concentration. It followed that the intermediate undergoing cyclization was simultaneously taking up another Na/e to eventually give the secondary alcohol. This crucial evidence taken in conjunction with (i) the 1:1 reduction/recovery ratio found at the same time, (ii) the failure of these compounds to give reduction products with $C_{10}H_8Na$/THF and Na/THF, and (iii) the formation of 5α,6,6-trideuterated 4,5-secocholestan-5β-ol from 6,6-dideuterated 4,5-secocholestan-5-one on treatment with Na/NH_3/THF has been used to distinguish between alternative mechanisms of alkali metal/NH_3 reductions of enolizable ketones. All except the vicinal dianion stand excluded. Two alternatives are proposed for its subsequent behavior. Alkali metal/NH_3 reductions of α,β-unsaturated ketones are also considered as proceeding via dianions. By extending the study to 4,5-secocholest-3-yn-5-one (**1a**) and 4a,5-seco-*A*-homocholest-4(4a)-yn-5-one (**1c**) the reactivity to cyclization via a 5-ketyl has been shown to be **1a** > **1c** > **1b** > **4**.

The mechanism of reduction of ketones by alkali metals in alcohols, ethers, and ammonia undoubtedly involves the formation of a radical anion in the first step. No agreement exists as to the sequence of addition of the remaining

0022-3263/81/1946-2633$01.25/0

Table I. Reaction of Ketone 1b with Na in NH_3/THF[a]

run	[ketone],[b] M	[Na],[b] M	[Na][b]/[ketone][b]	time, min	ratio[c] redn/rec	ratio[c] redn/cycl	redn/(cycl × [Na][b])
1	0.011	0.089	8.1	15	1.00	2.22	24.94
2	0.0055	0.086	15.6	15	1.05	2.44	28.37
3	0.016	0.087	5.4	15	1.05	2.40	27.59
4	0.021	0.084	4.0	10	1.03	2.30	27.38
5	0.011	0.098	8.9	5	0.98	2.79	28.47
6	0.011	0.055	5.0	5	1.03	1.78	32.36
7	0.078	0.072	9.2	5	1.02	2.12	29.44
8	0.016	0.088	5.5	4	1.00	2.47	28.28
9	0.022	0.055	2.5	0.25	0.42	1.67	30.36
10[d]	0.021	0.088	4.2	1[e]	0.89	1.22	
11[d]	0.021	0.143	6.8	3[e]	1.82	2.50	

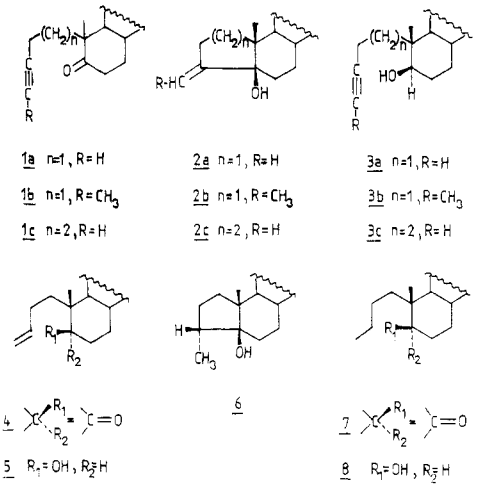
[a] NH_3/THF ratio of 4:1. [b] Initial concentrations. [c] Ratios of reduction, recovery, and cyclization based on the quantities of **3b**, **1b**, and **2b**, respectively, as obtained after chromatographic separation. [d] NH_3/THF/*t*-BuOH ratio of 4:0.8:0.2. [e] Unlike the other cases where sodium benzoate was used for quenching, here the blue color discharged by itself by the time given.

electron and two protons. The proposal by House[1] that protonation occurs next has gained relatively wide acceptance. But the applicability of this mechanism when proton donors other than substrate and NH_3 are absent has been questioned in recent years.[2,3] Precisely under such conditions we[4] have obtained reductive cyclization products formed by attack on acetylenic and olefinic groups by radical anions. The work reported in the previous paper includes an interesting observation. Only in a limited number of cases was reductive cyclization accompanied by simple reduction. The relative amounts of the three compounds corresponding to cyclization,[5] reduction, and recovery were dependent on the reaction conditions. A systematic study including an indirect determination of relative rates was hence undertaken in an effort to resolve the above outstanding issue.

Results.

The compounds discussed in the present work are all given in Chart I.[6] Most of these have been reported in the previous paper. Others were made by standard methods. The study of reduction began to make headway only after conditions were found for Na/NH_3 reductions wherein **1a** gave **2a** and **3a** free of any overreduction product. The absence of 3-methyl-*A*-norcholest-3(5)-ene was the surest indication that NH_3 was anhydrous and free of proton donors other than itself and the substrate.[7] The bulk of the work was done on **1b** and **4** as the most acidic protons in these were α to a ketone. Preliminary results indicated the need to confine the work to a single metal and a single cosolvent. Thus Na/NH_3/THF was used with a 4:1 ratio of NH_3/THF. Each product was obtained pure by chromatography and identified. Material balance after chromatography was between 90% and 96%, justifying

Chart I



semiquantitative evaluation. As reported in the previous paper,[4] **1b** gave two cyclized products, the *E* and *Z* isomers collectively described as **2b**, and one reduction product, **3b**, accompanied by recovery of starting material. No other compounds were produced as seen by TLC. The primary consideration was the ratio of reduction to cyclization and the relevance of this to the relative rates of these reactions. Rate-determining formation of a vinyl radical has been amply demonstrated for the cyclization reaction.[4] The role of the attacking species has been ascribed to the ketyl radical anion as it is the first intermediate to be formed reversibly by electron or alkali metal transfer to substrate.[2,3] The same intermediate is common to all the mechanisms that have been proposed for ketone reductions using alkali metal/NH_3. All these have an irreversible step at some stage. Since the same is true for cyclization, it follows that the ratio of rate of reduction to rate of cyclization could be equated to the ratio of the *amount* of reduction product to the *amount* of cyclization product obtained in the reaction.[8]

A relationship between this ratio and the concentration of substrate and electron/alkali metal[9] was sought. Practical necessities, including the need to avoid the bronze

(1) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, CA, 1972, pp 152–8.
(2) V. Rautenstrauch and M. Geoffrey, *J. Am. Chem. Soc.*, **99**, 6280–6 (1977).
(3) C. A. Young and R. R. Dewald, *J. Am. Chem. Soc.*, 101, 2884–7 (1979).
(4) S. K. Pradhan, S. R. Kadam, J. N. Kolhe, T. V. Radhakrishnan, S. V. Sohani, and V. B. Thaker, *J. Org. Chem.*, preceding paper in this issue.
(5) "Cyclization" in this paper is used to denote reductive cyclization. Reduction invariably means formation of secondary alcohol from ketone with all other functional group remaining unaffected. Recovery may or may not be via enolate anion.
(6) Partial formulas are used in Chart I. All compounds are cholestane derivatives.
(7) The test is not so sensitive with **1b** as with **1a** since overreduction of **2b** is considerably slower than that of **2a**.
(8) T. S. Lee, "Technique of Organic Chemistry", Vol. VIII, S. L. Friess and A. Weissberger, Eds., Interscience, New York, 1953, pp 100–30.
(9) Dewald[8] proposes one-electron followed by sodium cation addition in *pre*-rate-determining steps followed by electron addition in the rate-determining one. The kinetics do not rule out sodium cation plus electron (i.e., sodium atom) addition to a cation-free radical anion in the rate-determining step.

Table II. Reduction of Ketone 4 with Na in NH_3/THF[a]

run	[ketone],[b] M	[Na],[b] M	[Na][b]/[ketone][b]	time, min	ratio[c] redn/rec	ratio[c] redn/cycl	redn/(cycl × [Na][b])
1	0.038	0.099	2.6	15	1.10	5.47	55
2	0.016	0.045	2.8	10	0.95	1.92	43
3	0.010	0.096	9.6	5	1.08	4.59	48
4	0.016	0.103	6.4	0.33	0.72	5.16	50
				5	0.96	4.72	46
5	0.015	0.045	3.0	0.33	0.61	2.28	51
				5	0.94	2.00	44
6	0.0084	0.060	7.1	5	1.07	2.62	44
7[d]	0.016	0.051	3.2	2[e]	1.21	3.35	

[a,b,d,e] Refer to corresponding footnote in Table I. [c] Ratio of reduction, recovery, and cyclization based on quantities of **5**, **4**, and **6**, respectively, as obtained after chromatographic separation.

Table III. Reduction of Ketones 1a and 1c with Na in NH_3/THF[a]

compd (run)	[ketone],[b] M	[Na],[b] M	[Na][b]/[ketone][b]	time, min	ratio[c] redn/rec	ratio[c] redn/cycl	redn/(cycl × [Na][b])
1a (1)	0.016	0.104	6.5	0.3	0.90	0.231	2.22
				5	0.89	0.219	2.11
1a (2)	0.016	0.121	7.6	0.3	0.88	0.304	2.51
				5	0.94	0.304	2.51
1a (3)	0.016	0.071	4.4	0.3	0.83	0.176	2.48
				5	0.92	0.190	2.68
1c (4)	0.016	0.068	4.3	0.3	0.88	0.459	6.75
				5	0.88	0.438	6.44

[a,b] Refer to corresponding footnote of Table I. [c] Reduction and cyclization of 1a give **3a** and **2a** whereas 1c gives **3c** and **2c**.

phase,[10] required that only a limited excess of sodium be used and permitted only a semiquantitative evaluation. In spite of such limitations, satisfactory results were obtained. These are presented in Tables I and II and clearly establish the existence of the following relationship, where $k_r/k_c = 28.6 \pm 4.0$ and 48 ± 7 for **1b** and **4**, respectively.

$$\frac{\text{amt of reduction}}{\text{amt of cyclization}} = \frac{k_r[\text{intermediate}][\text{Na}]}{k_c[\text{intermediate}]} = \frac{k_r[\text{Na}]}{k_c}$$

Besides its bearing on the mechanism, a very useful consequence of this is that yields of cyclization relative to reduction can be increased dramatically by reducing the alkali metal concentration.[11]

The data in column six of the tables demonstrate the existence of an almost 1:1 relationship between reduction and recovery provided the time given was between 4 and 15 min. The last run in each table shows an excess of reduction. This is due to the presence of a proton donor and underlines the need to avoid the use of proton donors for quenching.

The proportionality constant of 48 ± 7 obtained for **4** is larger than that obtained with **1b**. The environment of the ketone group is very similar in both compounds, and hence a near identity of k_r can be expected for both. Thus k_c for **1b** can be estimated as being almost twice k_c for **4**. Hence, subject to the assumption of identity in rates of reduction, rough estimates of relative rates of cyclization were available provided the proportionality constant could be determined. Table III gives the results from **1a** and **1c** both of which have a terminal alkyne function. The order of reactivity as far as cyclization is concerned can thus be indicated as **1a > 1c > 1b > 4**.

In all these reductions the origin of the proton that became part of the secondary alcohol group was a matter of importance. Preliminary work showed that after deuteration compound **1b** gave an alcohol in which practically all the hydrogen at C-5 had been replaced by deuterium. In order to obtain definitive evidence, we prepared **7** and deuterated it with $CH_3OD/NaOCH_3$. The ketone having 95% d_2 and 5% d_1 as determined by mass spectroscopy was reduced with Na/NH_3/THF as usual. The reduction/recovery ratio was 1:1. The alcohol, deuterated **8**, was converted to a methanesulfonate to enable convenient determination of the extent of deuterium present at C-5 by NMR with reference to the methyl of the sulfonate. The number of atoms of hydrogen estimated to be present at C-5 was 0.15 ± 0.1. From the mass spectrum the alcohol was shown to have 80% d_3 and 20% d_2.

The availability of **7** led us to clarify a point related to the present work. Both **1b** and **4** had given cyclization products unaccompanied by reduction products when stirred for 70 h with Na or Li in THF at room temperature. Thus, doubt arose as to whether reduction is capable of proceeding at all under these conditions[12] even if there was no competition with cyclization. Reaction of **7** with Na in THF gave the alcohol **8**. The ratio of reduction to recovery was 2.9:1. Use of Li gave a reduction/recovery ratio of 1:1, consistent with the greater stability of lithium enolates.[13]

Discussion of Mechanism of Reduction

Results obtained in the present study taken together with those described in the previous paper eliminate all except one of four possible mechanisms[14] given in Scheme

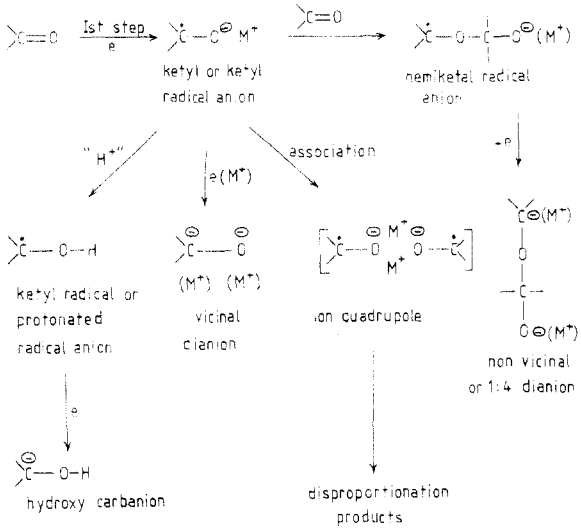
(10) M. Smith in "Reduction", R. L. Augustine, Ed., Marcel Dekker, New York, 1968, pp 95–170.

(11) G. Stork, R. K. Boeckmann, D. F. Taber, W. Clark Still, and J. Singh, *J. Am. Chem. Soc.*, 101, 7107–9 (1979), appear to have realized the need to keep the metal concentration low in order to get good yields in cyclization.

(12) Rautenstrauch[2] had reported extensive reduction as well as pinacolization in alkali metal reductions in THF solution at ca. −75 °C.

(13) J. d'Angelo, *Tetrahedron*, 32, 2979–90 (1976).

Scheme I



I. So far, convincing evidence in favor of any single one has been lacking.[15] The first step common to all mechanisms is the reversible formation of the ketyl radical anion.[16]

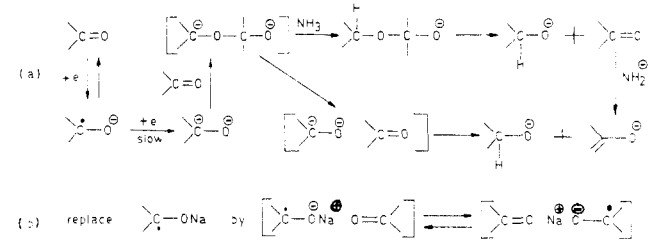
Studies on reductive cyclization of **1b** using naphthalene sodium in THF[17] and of **1b** and **4** using Na or Li in THF have shown[4] that attack on the multiple bond is by a "radical" at C-5. There is no evidence of simultaneous reduction under these conditions. This behavior is in striking contrast with that of 5-hexenyl radicals in the presence of naphthalene sodium.[18] Thus the "radical" at C-5 must be regarded as being relatively resistant to reduction to a carbanion with this reagent and only slowly reducible by Na or Li in THF. A radical anion at C-5 may be expected to be somewhat resistant to dianion formation, but the protonated radical anion or the hemiketyl radical anion has only to be reduced to a monoanion, a process generally accepted as proceeding at diffusion-controlled rates.[19]

As sodium in ammonia is a more powerful reducing system than naphthalene sodium in THF[17] and provides a greater concentration of electron/sodium than sodium in THF, much more rapid transfer of electron/sodium to the radical anion was likely. Hence it appeared reasonable to ascribe the isolation of the reduced product to the formation of dianion as had been envisaged by Barton.[14]

Definite evidence favoring this mechanism and excluding the others has now been obtained by establishing that for compounds **1b** and **4** the ratio of reduction to cyclization is dependent on sodium concentration alone.

This finding rules out the Rautenstrauch mechanism involving disproportion of an ion quadrupole[2] and also the slow addition of radical anion to ketone to give the hemiketyl radical anion. The House mechanism can also be

Scheme II[a]



[a] Counterions not shown for part a.

ruled out if protonation is by the ketone. Protonation by NH_3 is unlikely since the rate constant for proton abstraction by the ketyl radical anion from NH_3 is estimated[20] as being about 1×10^{-22} M^{-1} s^{-1}.

On the other hand, the observed dependency of the ratio is in complete agreement with a slow addition of electron/sodium to the ketyl radical anion to give the vicinal dianion. A similar postulate has been recently made by Dewald[3] on the basis of an excellent kinetic study of reduction of dimethylformamide by sodium in liquid ammonia. Thus it appears that a dianion associated with a sodium cation is formed even from the more difficultly reducible amide system.[21]

The vicinal dianion derived from 6,6-dideuterated 4,5-secocholestan-5-one gives 80% of a trideuterated alcohol, confirming the observation of Rautenstrauch[2] that substantial amounts of trideuterated alcohol are formed from 2,2-dimethyl-6,6-dideuterated cyclohexanone with sodium in liquid ammonia.

This finding can be accommodated in the post-rate-determining step. The vicinal dianion can be expected to be a very powerful nucleophile because of the "α effect".[22] The presence of an adjacent lone pair on the carbon can be expected to increase the nucleophilicity of the alkoxide considerably.[22] An FMO explanation[23] of this phenomenon provides a ready explanation as to why the corresponding radical anion cannot be expected to be anywhere near as reactive. The "dimeric" nonvicinal dianion and the vicinal dianion plus ketone can then be in equilibrium within a cage from which an enolate and alkoxide can emerge provided the ketone has protons α to the carbonyl group. Proton abstraction from NH_3 at carbon could be taking place to some extent. It may, however, be at a disadvantage since it amounts to a soft base abstracting a proton from a hard acid.[24] The overall picture is given in Scheme II.

It is possible that the vicinal dianion does not have to search out a ketone molecule from the solution. It could already be present in a cage with it *without* being covalently bonded. Such a possibility is indicated in Scheme IIb. Atom transfers of this kind are well-known.[25] Enough ketone should, however, be available. A necessary postulate is that cyclization as well as reduction occurs primarily from this intermediate. This would accommodate the ratio dependency observed in the present work. The choice between these two mechanisms differing in subtle details must await a kinetic study.

(14) D. H. R. Barton, *Experentia*, **6**, 316–29 (1950), proposed the vicinal dianion mechanism. The ketyl radical and the ion quadrupole mechanisms were proposed by House[1] and Rautenstrauch,[2] respectively. Intermediates analogous to the hemiketal radical anion were proposed by J. J. Bloomfield, D. C. Owsley, C. Ainsworth, and R. E. Robertson, *J. Org. Chem.*, **40**, 393–402 (1975).

(15) A survey of these mechanisms has been removed in the revision for the sake of compactness. It will be available in the Ph.D. Thesis (Bombay University) of J.N.K.

(16) No attempt has been made in the present work to discriminate between radical anion free of or associated with counterion.

(17) S. K. Pradhan, T. V. Radhakrishnan, and R. Subramanian, *J. Org. Chem.*, **41**, 1943–52 (1976).

(18) J. F. Garst and F. E. Barton II, *Tetrahedron Lett.*, 587–91 (1969).

(19) A. J. Fry, "Synthetic Organic Electrochemistry", Harper and Row, New York, 1972, p 208.

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The relevance of the present work to the alkali metal/NH_3/THF reduction of α,β-unsaturated ketones is obvious. Successive addition of two electrons to give a dianion must be even more facile than with saturated ketones. Equilibrium after the first addition can be expected to be so much toward the radical anion that practically no enone will be available to provide a proton to the dianion. Reaction of this with a proton from NH_3 could be a reversible process at oxygen and an irreversible one at carbon, thus accounting for the well-known observation about the source of the proton that attaches to the β-position. The radical anion derived from the enone should be an even weaker base than that derived from a ketone. So proton abstraction with NH_3 is out of the question. With the weaker reducing agent, naphthalene sodium, dianion formation from an enone was ruled out on the basis of work reported in the previous paper. Thus, 4,5-secocholest-5-en-3-yn-7-one gave products typical of a radical anion such as hydrodimerization and cyclization but no dihydro compounds. On the other hand, Na/NH_3/THF gave almost a quantitative yield of 4,5-secocholest-3-yn-7-one, indicating a very short half-life for the radical anion under these conditions. This constitutes very strong support for the Barton[26] proposal that dianions are intermediates in reductions of α,β-unsaturated ketones.

Experimental Section

General Methods. Infrared spectra were obtained with a Perkin-Elmer Model 397 double-beam spectrophotometer. NMR spectra were recorded on Varian EM 360 L spectrometer in CCl_4 with Me_4Si as an internal standard. Optical rotations were determined in $CHCl_3$ at room temperature with a Carl Zeiss Winkel spectropolarimeter. Melting points were determined in a VEB Analytic Dresden HMK melting point apparatus and are uncorrected. 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 h before use.

Ether was dried by keeping it overnight over fused $CaCl_2$ followed by distillation from Na and storage over Na. It was freshly distilled from LAH before use. *tert*-Butyl alcohol was dried by initial reflux over Na followed by distillation from $LiAlH_4$ or CaH_2. Benzene was dried over Na. Ethyl acetate was dried by distillation from P_2O_5. CH_3COOD was prepared by a standard method using D_2O and acetyl chloride and had 99% isotopic purity. The D_2O used contained 99.8 atom % deuterium, and the methanol-*d* used contained 99.0 atom % deuterium.

All reactions as well as column chromatography were followed by TLC using microslides, with detection by exposure to iodine vapor. Unless otherwise stated, the reactions were worked up as follows. The mixtures were poured into water and extracted twice with ether, and the combined ether extract was washed with dilute HCl followed by water and dilute bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was subjected to column chromatography over standard grade alumina or silica gel.

Reductions with Na/NH_3/THF. Special precautions described below were taken to ensure the anhydrous conditions. It was possible to test this by reducing **1a** and showing that no 3-methyl-*A*-norcholest-3-(5)-ene was produced. To obtain reproducible results, quantities were accurately measured, and timings for some of the stages were fixed. Only after this was the data given in the tables collected. The typical procedure is given below for **1b**.

A large volume of ammonia was first condensed in a glass vessel by using a dry ice/acetone condenser. To this was added excess sodium until a blue color persisted. This NH_3 was used for flushing the moisture-free reaction assembly. A positive pressure of this NH_3 was maintained throughout the reaction. A flat-bottomed, graduated, cylindrical, two-necked flask (parallel) provided with a magnetic stirrer was used for the reaction. To one neck was attached an adapter with a special compartment for storing Na under THF and an outlet for NH_3. The other neck was the inlet for anhydrous NH_3. After the system was flushed thoroughly, NH_3 was condensed by external cooling until 40 mL was collected. Previously weighed Na (66.91 mg, 2.9 mmol) kept in adapter under THF was transferred to the reaction vessel by using a fine needle pierced through a rubber septum. After 1 min of stirring to ensure the solution of the small amount of the alkali metal used, the stirring was stopped, a solution of 200 mg (0.5 mmol) of **1b** dissolved in 10 mL of THF was injected rapidly, and stirring was continued for 10 min. Then sodium benzoate was added. After evaporation of NH_3, the residue was extracted three times with ether and worked up as usual. Removal of ether and chromatography on silica gel gave 65 mg of starting material followed by 32 mg of mixture of (*E*)- and (*Z*)-3-ethylidene-*A*-norcholestan-5β-ols (**2b**) identical with that reported earlier. Finally, 67 mg of 4-methyl-4,5-secocholest-3-yn-5β-ol (**3b**) was obtained: mp 78–80 °C; $[\alpha]_D$ +12° (*c* 0.10).

Subsequently, the assembly was modified to permit transfer of about half of the reaction mixture into another compartment containing excess sodium benzoate in liquid NH_3. Thus an estimate of the progress of the reaction could be made over two time periods. By use of this assembly reproducibility was confirmed over a dozen runs before the work reported in the tables was carried out.

4,5-Secocholestan-5-one (7). A solution of 384 mg (1 mmol) of 4,5-secocholest-3-yn-5-one (**1a**) in 20 mL of ethyl acetate was mixed with a slurry of 38 mg of 10% palladium on carbon in 5 mL of ethyl acetate and hydrogenated in Parr hydrogenator at 1 atm pressure until it absorbed about 44 mL of H_2. The reaction mixture was filtered, and ethyl acetate was removed. The residue was filtered through silica gel with benzene as eluent to give 380 mg of 4,5-secocholestan-5-one (**7**) as an oil: $[\alpha]_D$ +38° (*c* 0.12); IR (neat) 2950, 1705 (C=O), 1460, 1375, 950 cm^{-1}; NMR (CCl_4) δ 0.73 (3 H, s, C-18 methyl), 1.00 (3 H, s, C-19 methyl). Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.37; H, 12.57.

Lithium Aluminum Hydride Reduction of 7. To a solution of 195 mg (0.5 mmol) of 4,5-secocholestan-5-one (**7**) in 10 mL of dry ether was added 57 mg (1.5 mmol) of LAH, and the mixture was stirred under a nitrogen atmosphere for 1 h. The reaction was quenched by dry ethyl acetate followed by a saturated aqueous solution of Rochelle salt. The solution was extracted as usual and chromatographed on silica gel with 1:1 benzene–hexane as eluent to give 15 mg of 4,5-secocholestan-5α-ol as an oil: $[\alpha]_D$ +46° (*c* 0.10); IR (Nujol) 3450 (OH), 2950, 1470, 1380, 1110, 990 cm^{-1}; NMR (CCl_4) δ 0.67 (3 H, s, C-18 methyl), 0.9 (3 H, s, C-19 methyl), 3.53 (1 H, br, $W_{1/2}$ = 9 Hz, C-5 H). It was not further characterized.

Later fractions gave 175 mg of 4,5-secocholestan-5β-ol (**8**) as a white solid: mp 62–63 °C; $[\alpha]_D$ +22° (*c* 0.10); IR (Nujol) 3450, 2950, 1470, 1385, 1040, 985 cm^{-1}; NMR (CCl_4) δ 0.83 (3 H, s, C-18 methyl), 0.93 (3 H, s, C-19 methyl), 3.37 (1 H, m, $W_{1/2}$ = 18 Hz, C-5 H). Anal. Calcd for $C_{27}H_{50}O$: C, 83.00; H, 12.90. Found: C, 82.89; H, 12.71.

The mesylate of **8** was prepared by stirring a solution of 195 mg (0.5 mmol) of **8** in 1 mL of pyridine with 0.08 mL of methanesulfonyl chloride for 1 h; the reaction mixture was extracted in $CHCl_3$. The chloroform layer was washed with dilute HCl followed by water and finally dried over anhydrous sodium sulfate. Removal of chloroform gave 200 mg of the corresponding mesylate as a thick gum: $[\alpha]_D$ +17° (*c* 0.127); IR (neat) 2980, 1460, 1320, 1170, 910, 900, 740, 570, 495 cm^{-1}; NMR (CCl_4) δ 0.63 (3 H, s, C-18 methyl), 0.87 (3 H, s, C-19 methyl), 2.87 (3 H, s, OSO_2CH_3), 4.53 (1 H, m, $W_{1/2}$ = 18 Hz, C-5 H). Anal. Calcd for $C_{28}H_{52}O_3S$: C, 71.74; H, 11.18. Found: C, 72.26; H, 10.89.

Action of Na/NH_3 on 7. To a stirred solution of 72.5 mg (3.15 mmol) of sodium in 40 mL of redistilled, anhydrous ammonia was added a solution of 340 mg (0.87 mmol) of 4,5-secocholestan-5-one (**7**) in 10 mL of dry THF. After 4 min the reaction was quenched with sodium benzoate and worked up as usual. Chromatography on silica gel with 1:1 benzene–hexane as eluent gave initially 169 mg of starting material followed by 172 mg of 4,5-secocholestan-5β-ol (**8**), identical in all respects with the major product obtained on LAH reduction of **7**.

(26) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045–51 (1954).

Reaction of 7 with NaOD in D_2O/THF could not give quantitative deuterium exchange at C-6. Thus quantitative deuteration was achieved by reducing the corresponding dibromide with Zn/CH_3COOD in dry ether.

6,6-Dibromo-4,5-secocholestan-5-one. To a stirred solution of 390 mg (1 mmol) of 4,5-secocholestan-5-one (7) in 15 mL of chloroform was added a solution of 352 mg (4.4 mmol) of Br_2 in 15 mL of $CHCl_3$ containing few drops of 40% HBr. After 1 h, the reaction mixture was extracted in $CHCl_3$. The chloroform layer was washed with saturated bicarbonate followed by saturated thiosulfate and finally dried over anhydrous sodium sulfate. Removal of chloroform and chromatography of residue on silica gel with hexane as eluent gave 500 mg of 6,6-dibromo-4,5-secocholestan-5-one as thick gum: $[\alpha]_D$ −73.29° (*c* 0.0993); IR (neat) 2950, 1725 (C=O) 1460, 1380, 1200, 1000, 660 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.42 (3 H, s, C-19 methyl), 2.73 (2 H, dd, J = 13, 9 Hz, C-7 H). Anal. Calcd for $C_{27}H_{46}OBr_2$: C, 59.34; H, 8.49. Found: C, 59.60; H, 8.65.

Debromination of 6,6-Dibromo-4,5-secocholestan-5-one with Zn/CH_3COOD. To a stirred solution of 548 mg (1 mmol) of 6,6-dibromo-4,5-secocholestan-5-one in 10 mL of dry ether was added 650 mg (10 mmol) of freshly activated Zn dust and 1.20 g (20 mmol) of CH_3COOD, and the mixture was stirred under nitrogen for 3 h. The reaction mixture was filtered under a nitrogen atmosphere, and the filtrate was washed with D_2O (3 × 1 mL). Dry benzene (100 mL) was added, and the organic solvent was removed to yield 350 mg of 4,5-secocholestan-5-one-6-d_2. This was reduced in part by $LiAlH_4$ as reported earlier to give 4,5-secocholestan-5β-ol which indicated that most of the C-6 H was exchanged. Further enrichment of deuterium was done as follows. A solution of NaOD in CH_3OD/D_2O was prepared by addition of 5 mg of NaH to a solution of 1 mL of D_2O in 2.5 mL of CH_3OD which was then added to the above-obtained 6-d_2 ketone, and the mixture was refluxed under nitrogen for 6 h. Dry benzene was added, and the D_2O layer was removed by syringe. After removal of benzene, the treatment was repeated three times to give about 97% deuterium at C-6 as shown by the mass spectrum.

Action of Na/NH_3 on 4,5-Secocholestan-5-one-6-d_2. To a stirred solution of 65.13 mg (2.8 mmol) of sodium in 40 mL of anhydrous and redistilled ammonia was added a solution of 300 mg (75.63 mmol) of 4,5-secocholestan-5-one-6-d_2 in 10 mL of THF. After 4 min, the reaction was quenched by sodium benzoate. NH_3 was evaporated, and the residue was extracted in ether as usual. Chromatography on silica gel with 1:1 benzene–hexane as eluent gave initially 112 mg of 4,5-secocholestan-5-one (7). It was reduced by LAH to yield the corresponding 5β-ol, which indicated 55.21% of monodeuterated and 44.79% nondeuterated compound by mass spectrum.

Later fractions gave 110 mg of 4,5-secocholestan-5β-ol. The mass spectrum of this alcohol showed 80.29% of trideuterated and 19.71% of the dideuterated compound. This alcohol was mesylated as reported earlier, and its NMR spectrum indicated the presence of 15% H at C-5. The rest of the substituent must be deuterium. The C-5 H signal was practically a singlet, indicating that the proton content at C-6 is not more than marginal.

Na/THF on 4,5-Secocholestan-5-one (7). To a solution of 400 mg (1.03 mmol) of 7 in 8 mL of dry THF was added 94.5 mg (4.11 mmol) of freshly cut sodium under a nitrogen atmosphere, and the mixture was stirred for 70 h. The reaction mixture was filtered from unreacted sodium, and the filtrate was extracted in ether as usual. Chromatography of the residue on silica gel with 1:1 benzene–hexane as eluent gave 90 mg of the starting ketone followed by 263 mg of 4,5-secocholestan-5β-ol (8), identical in all respects with the authentic sample. Finally, 31 mg of oily compound was obtained: IR (CCl_4) 3450, 1460, 1370, 1250, 1140 cm^{-1}; NMR (CCl_4) δ 0.67 (s, C-18 methyl), 0.93 (s, C-19 methyl). It was not characterized further.

Action of Li/THF on 7. To a solution of 460 mg (1.18 mmol) of 7 in 8 mL of dry THF was added 30 mg (4.3 mmol) of freshly cut lithium under a nitrogen atmosphere, and the mixture was stirred for 70 h. The reaction mixture was worked up as above, and the residue was chromatographed on silica gel with 1:1 benzene–hexane as eluent to give 221 mg of the starting ketone followed by 218 mg of the corresponding 5β-ol 8. Finally, 12 mg of a compound was obtained which was not characterized.

Acknowledgment. We are grateful to Nivedita Chemicals Pvt. Ltd. for a generous gift of dry ice, to the Chemistry Department, Pune University, for C and H analysis, and to Schering Corp. for mass spectra. We are grateful for fellowships awarded by the University Grants Commission to S.R.K. and by the Council of Scientific and Industrial Research to J.N.K.

Registry No. **1a**, 21489-86-1; **1b**, 58502-98-0; **1c**, 58503-18-7; **2a**, 21489-85-0; (*E*)-**2b**, 58503-11-0; (*Z*)-**2b**, 58503-12-1; **2c**, 58503-19-8; **3a**, 32232-84-1; **3b**, 58503-16-5; **3c**, 77071-07-9; **4**, 77071-08-0; **5**, 77071-09-1; **6**, 77071-10-4; **7**, 77071-11-5; **8**, 77071-12-6; **8** mesylate, 77071-13-7; 6,6-dibromo-4,5-secocholestan-5-one, 77071-14-8; 4,5-secocholestan-5-one-6-d_2, 77071-15-9; 4,5-secocholestan-5α-ol, 77071-16-0; sodium, 7440-23-5.