Registry No.—I, 20859-13-6; II, 29569-89-9; III, 141-79-7; IV, 565-62-8; V, 625-33-2; VI, 94-41-7; VII, 98-53-3; VIII, 873-94-9; $LiAlH_4$, 16853-85-3; AlH_3, 7784-21-6; H_2AlI, 58602-50-9; $HAlI_2$, 58602-51-0; H_2AlCl, 14644-71-4; $HAlCl_2$, 13497-97-7; CuI, 7681-65-4; $TiCl_3$, 7705-07-9; HgI_2, 7774-29-0; $HgCl_2$, 7487-94-7; CuCl, 7758-89-6.

References and Notes

(1) R. L. Augustine et al., *J. Org. Chem.*, **34**, 1074 (1969).
(2) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, p 173.
(3) (a) R. K. Boeckman, Jr., and R. Michalak, *J. Am. Chem. Soc.*, **96**, 1623 (1974); (b) S. Masamune, G. S. Bates, and P. E. Georghiou, *ibid.*, **96**, 3686 (1974).
(4) B. Ganem, *J. Org. Chem.*, **40**, 146 (1975).
(5) H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969).
(6) E. C. Ashby and B. Cooke, *J. Am. Chem. Soc.*, **90**, 1625 (1968), and references cited therein.
(7) S. Masamune, P. A. Rossy, and G. S. Bates, *J. Am. Chem. Soc.*, **95**, 6452 (1973).
(8) J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, **96**, 4708 (1974).
(9) To be reported in more detail shortly.
(10) D. L. Schmidt and E. E. Flagg, *Inorg. Chem.*, **6**, 1262 (1967).
(11) E. C. Ashby and R. D. Schwartz, *J. Chem. Educ.*, **51**, 65 (1974).
(12) H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770 (1975).

A Study of the Stork Reductive Cyclization of Steroidal Acetylenic Ketones in Aprotic Media with the Naphthalene Anion Radicals

Suresh K. Pradhan,* Tarur V. Radhakrishnan, and Raman Subramanian

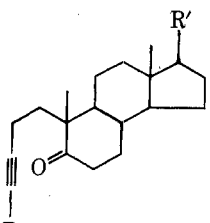
Pharmaceutical Section, Bombay University, Department of Chemical Technology, Bombay 400.019, India

Received February 9, 1976

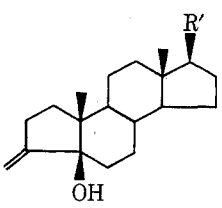
Reductive cyclization of steroidal acetylenic ketones was achieved in THF or DME with $C_{10}H_8{\cdot}^-M^+$. From 4,5-secocholest-3-yn-5-one (**1a**) the allylic alcohol 3-methylene-*A*-norcholestan-5β-ol (**2a**) is the sole product. With this reagent no overreduction occurs. Recovery of starting material was proved to be due to competitive enolate ion formation. Ratio of reductive cyclization to recovery varied with solvent and counterion as well as with substrate. In a series of 4,5-secocholestan-5-ones the substituent at 10α was varied from $-(CH_2)_2C{\equiv}CH$ (**1a**) and $-(CH_2)_2$-$CH_2C{\equiv}CH$ (**25**) to $-(CH_2)_2C{\equiv}C-CH_3$ (**1c**). The observed ratios were 2.3, 8.2, and 0.7, respectively. In each case, the cyclization was regiospecific leading exclusively to an exo double bond. Kinetic control was established when **25** showed the same stereoselectivity as the others and gave an A:B cis product. The formation of different products from **25** and **1c** eliminated allene intermediates. With **1c** the stereochemistry of addition across the acetylene was syn:anti equal to 52:48. This shifted to >80% syn for **5e**. Based on available data, a mechanism is proposed. Electron is transferred preferentially, though reversibly, by $C_{10}H_8Na$ to the ketone group to give a ketyl radical ion. In the next slow step, this attacks the acetylene intramolecularly, as a radical and not as a nucleophile. Equilibration of the resulting vinyl radical with its isomer precedes reduction and protonation to the allyloxy anion precursor of the cyclized product. The initial addition across acetylene is syn. This follows from the change in syn:anti ratio to 70:30 when **1c** is added to excess reducing agent.

The reductive cyclization of γ-ethynyl ketones to allylic alcohols with alkali metals in liquid ammonia was first reported by Stork.[1] In a slightly modified form, this reaction was used for making interesting *A*-nor sterols.[2] The reaction was found to be stereoselective. Thus, the only products obtained from 4,5-secocholest-3-yn-5-one (**1a**) were 3-methylene-*A*-norcholestan-5β-ol (**2a**) and 3-methyl-*A*-norcholest-3-ene (**3a**). The latter was a product of overreduction. With NH_4Cl as a proton source, **3a** was the only product. With *t*-BuOH under carefully controlled conditions, mixtures of **2a** and **3a** resulted. Even under these conditions, **1b** gave only **3b.**

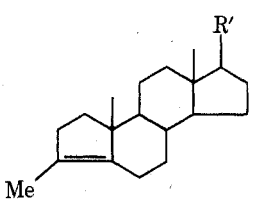
It was expected that overreduction could be avoided with a milder reducing agent used in combination with an aprotic medium. When preliminary work[3] indicated that naphthalene sodium in THF could serve the purpose, a deeper study into several aspects of this reaction was undertaken and is the subject of the present report.[4]



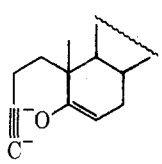
1a, R = H; R′ = C_8H_{17}
b, R = H; R′ = OH
c, R = Me; R′ = C_8H_{17}



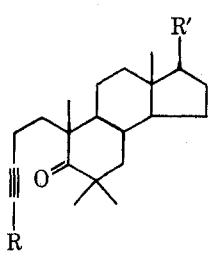
2a, R′ = C_8H_{17}
b, R′ = OH
c, R′ = OMe



3a, R′ = C_8H_{17}
b, R′ = OH



4



5a, R = H; R′ = C_8H_{17}
b, R = H; R′ = OH
c, R = H; R′ = OMe
d, R = Me; R′ = C_8H_{17}
e, R = D; R′ = C_8H_{17}

A solution of the acetylene ketone **1a** in THF or DME was

titrated with the dark green concentrated solution (0.6 N) of the naphthalene radical anion ($C_{10}H_8\cdot^-$, M^+) in THF or DME to a faint green end point. Each mole of sterol **1a** required 2.0 ± 0.2 mol of reagent and gave 70% **2a** and 30% **1a.** It was a very clean reaction amenable to semiquantitative evaluation. Hence the effect on the yield of changes in counterion and solvents could be studied. The results are given in Table I.

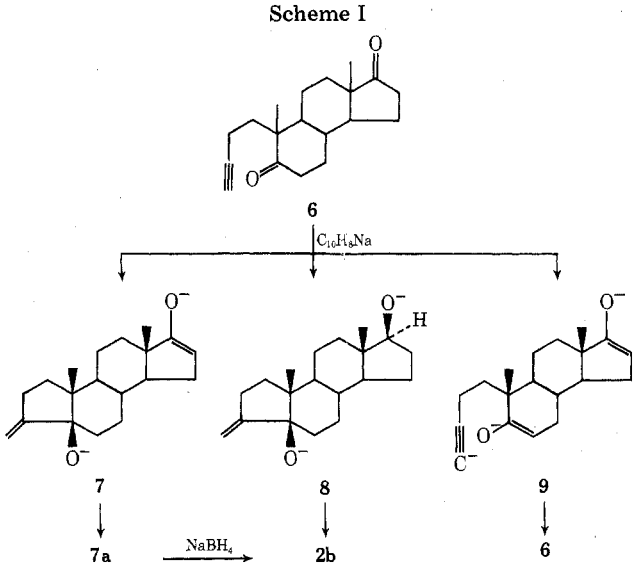
Electron transfer from sodium using naphthalene as a catalyst could also be achieved leading to formation of **2a** in 90% yield. However, the reaction was much slower. Details of the catalytic use of naphthalene are given in the Experimental Section. The rest of this article is concerned only with the very fast reactions which took place on titration with preformed reagent. The yields of **2a** were not noticeably affected by reversing the mode of addition or by lowering the temperature to 0 °C.

Recovery of 30% starting material could be reconciled with consumption of 2 mol of reagent by taking into account the dual behavior of the aromatic radical ions first noted by Scott.[5] They reduce halides by electron transfer but the same reagents act exclusively as strong bases when they react with alcohols. It was obvious that this dual behavior is being demonstrated in a 7:3 ratio with the steroidal substrate. Proton abstraction leads to dianion **4** which regenerates starting material on workup. Formation of the enolate ion was confirmed by adding excess methyl iodide prior to workup. In this case, **2a** was accompanied by the 6,6-dimethyl derivative **5a**[7] to the exclusion of **1a.** The removal of proton from acetylene was confirmed by quenching with deuterioacetic acid.

Reductive cyclization with $C_{10}H_8Na$ was carried out successfully with three distinct types of acetylene ketones. In every case, stereochemistry was established and has yielded information having a significant bearing on the mechanism of this reaction.

Terminal γ-Ethynyl Ketones. Results with **1a** are given in Table I. The 17β-hydroxy compound **1b** was of special interest since it had given only the overreduction product **3b** under protic conditions.[2] With naphthalene sodium **2b** was the only product but separation from **1b** was not possible. Addition of methyl iodide prior to workup gave **2c** and **5c.**[8] The desired **2b** was more conveniently obtained starting from the acetylene dione **6** as shown in Scheme I. All these cyclizations were stereoselective, leading to A:B cis products, and regiospecific, giving only a five-membered ring.

Scheme I



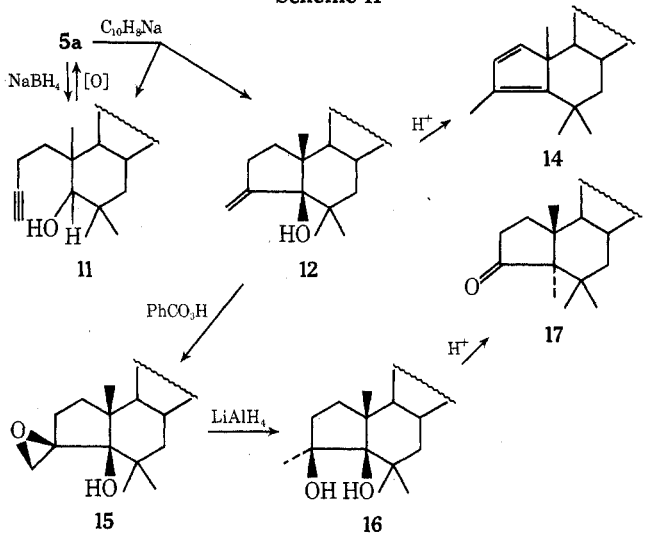
Cyclization of the 6,6-dimethyl derivative **5a** was of interest in view of steric hindrance at and nonenolizability of the ketone group. Reaction of **5a** with $C_{10}H_8Na$ gave 60% **12** and 40% **11.**[9] The latter could also be obtained by borohydride reduction of **5a.** The structure and stereochemistry of **12** were determined as shown in Scheme II.[10] The stereochemistry of **12**

Table I. Effect of Solvent and Counterion on the Reaction of 1a with $C_{10}H_8\cdot^-$

Counter-ion	Sol-vent[a]	2a	1a[b]	Counter-ion	Sol-vent[a]	2a	1a[b]
K^+	THF	69[c]	30	K^+	DME	64[c]	35
Na^+	THF	69	27	Na^+	DME	65	31
Li^+	THF	42	45	Li^+	DME	38	50

[a] 0.6 N reagent was used. [b] Recovery via enolate ion 4. [c] Percentage yields are given based on weights of material isolated by column chromatography.

Scheme II



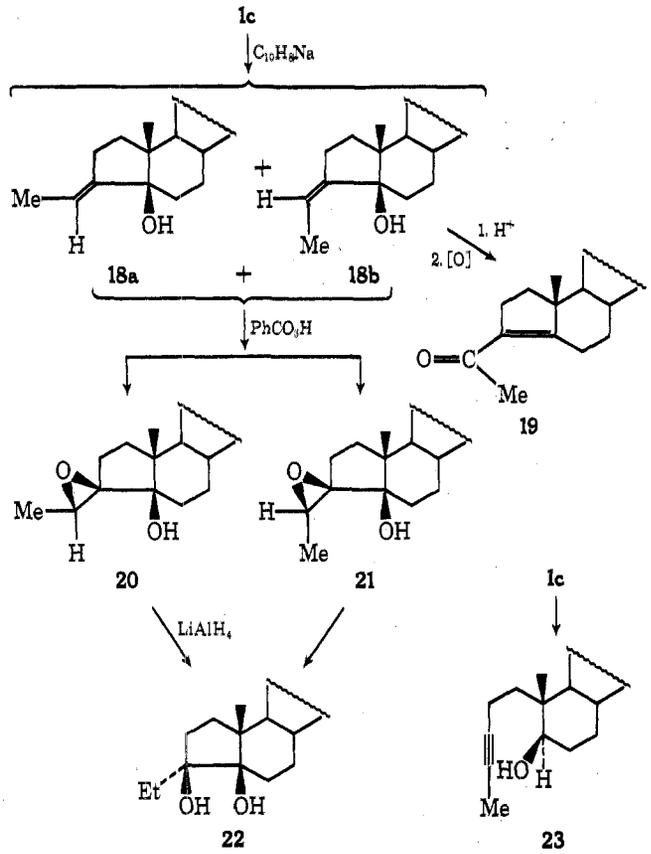
was indicated by NMR to be the same as in **2a** but was independently confirmed since substitution so close to the reacting center could have altered it. The proof consists of stereospecific conversion to **17** having an A:B trans junction as confirmed by its "negative Cotton effect".[11] In this cyclization, there was no recovery of starting material, lending support to the view that survival of ketone from reductive cyclization or reduction is due to enolate ion formation.

The possibility of determining the stereochemistry of addition across the acetylene was opened up by a comparison of the NMR of **12** and **2a.** The exocyclic methylene in the former gave two broad singlets at δ 4.98 and 5.25 whereas the latter gives a multiplet at δ 5.1 ppm. The deshielding of one of the exo protons in the dimethyl series was particularly marked in the epoxidation products. In the NMR of **15** the two protons were at δ 2.75 and 3.48 as compared to δ 2.96 and 3.00, respectively, in the unmethylated compound.[2]

The deshielding is ascribed to steric compression[12] since models showed close proximity of the α-methyl at C-6 to the exo hydrogen cis to C-5. This information was put to use by replacing the acetylenic hydrogen in **5a** by deuterium to give **5e** prior to reductive cyclization. The deuterated **12** produced in this reaction was analyzed by NMR for deuteration at the vinylic position. It could be estimated that 0.8–0.75 atoms of deuterium were present at the exo position cis to C-2, while 0.0–0.2 were at the position cis to C-5. Even this approximate estimation allows the conclusion that, in this case, addition across the acetylene is predominantly syn. The other product of this reaction, **11**, was free from deuterium. The significance of the finding is discussed below.

Nonterminal γ-Ethynyl Ketones. The methyl acetylene ketone **1c** was prepared from 4-methylcholest-4-en-3-one and treated with $C_{10}H_8Na$ to give only two spots on TLC. One corresponded to starting material but addition of methyl iodide prior to workup led to its conversion to the 6,6-dimethyl derivative **5d**. The other spot had an R_f value quite distinct from that of **23** (the major borohydride product of **1c**). It represented a mixture of two compounds obtained in 42% yield. These (**18a** + **18b**) could not be separated but structure and configuration could be assigned on the basis of work summarized in Scheme III.

Scheme III

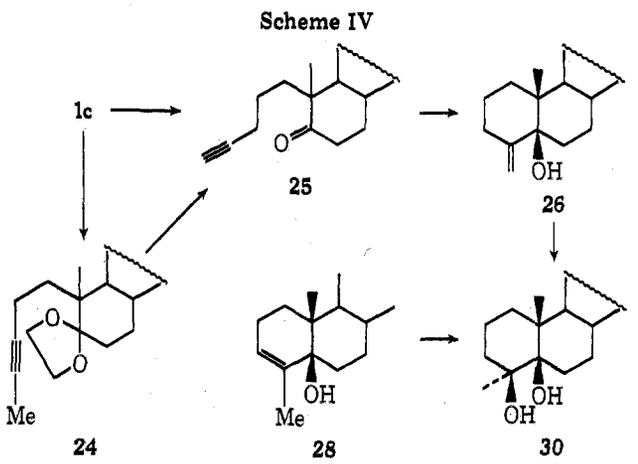


The spectral evidence for the structure of **19** was quite conclusive. Conversion of **20** and **21** individually to the same diol **22** on $LiAlH_4$ reduction established that the stereochemistry at the A:B ring junction was the same in **18a**, **18b**, **20**, **21** and **22**. NMR comparison of these with closely related compounds of established structures[2] with particular reference to the chemical shift of the 19-methyl confirmed that the A:B ring junction must be cis in all. Hence **18a** and **18b** must be stereoisomeric around the double bond. It was essential to determine the relative amounts of the two isomers and if possible their stereochemistry. Since epoxidation yields were quantitative, it could be assumed that information about the relative amounts of **20** and **21** could be extrapolated back. Since **20** and **21** could be separated, it was possible to establish that the isomeric alcohols **18a** and **18b** were in the proportion of 58(±3):42(±3). Thus, *substantial quantities* of both isomers are being produced. Hence there is only marginal preference for syn or anti addition across the acetylene in this case. This significant finding is not dependent on correct assignment of configuration to **18a** and **18b**. A tentative assignment is possible because the methyl doublet in **21** can be expected to be downfield relative to that in **20** because of steric compression. The major isomer has this doublet at δ 1.28 in the NMR whereas the minor one has it at δ 1.50 ppm. Hence, it can be tentatively concluded that syn addition across the acetylene to give **18a** is marginally preferred to anti addition giving **18b**.

The reaction is, however, regiospecific in that no six-membered ring formation is detected.[13] Compound **1c** was converted into the borohydride reduction product **23** on the one hand and the ketal **24** on the other. Both of these were subjected independently to reductive cyclization conditions to obtain evidence for acetylene reduction. They were both quantitatively recovered.

Terminal δ-Ethynyl Ketone. The homologous acetylene ketone **25** was required for distinguishing between kinetic and thermodynamic control. It was made by isomerization of **1c**. The isomerization was carried out by $NaNH_2$ generated in situ by bubbling NH_3 gas into $C_{10}H_8Na$ in THF[14] till the color was discharged. The THF was replaced by toluene and then refluxed. Yields of the rearranged product **25** were not satisfactory. Suspecting fragmentation, we protected the ketone as the ketal **24** prior to isomerization. The yield of **25** improved. Cyclization of this with $C_{10}H_8Na$ gave 89% **26** and 11% **25**. The structure **26** is consistent with spectral data whereas its stereochemistry was established by direct correlation[15] as shown in Scheme IV. The diol **30** is identical with one of the

Scheme IV



two cis diols obtained by the action of OsO_4 on 4-methylcholest-4-ene.

The cyclization of **25** is highly stereoselective giving exclusively an A:B cis product. In common with the other systems, it also shows regiospecificity.

Discussion

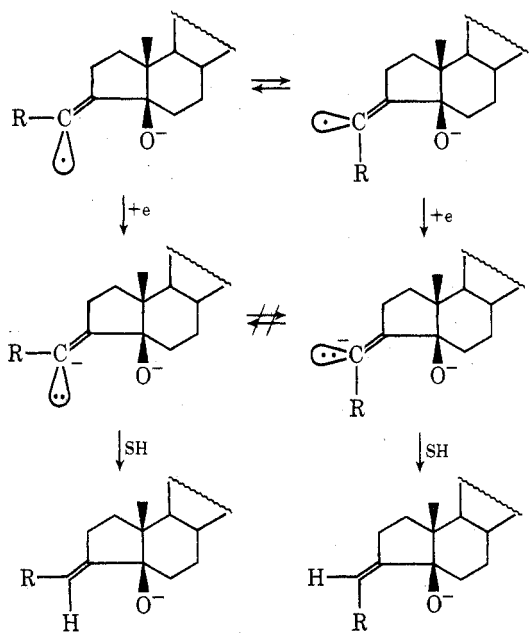
From the preparative point of view, the reductive cyclizations reported here are extensions of the reaction discovered by Stork. The present reagent offers several advantages, the foremost being that no overreduction takes place. The stereochemical findings give an insight into the mechanism and are hence briefly summarized here. Reductive cyclization of the 5-keto sterols invariably gave an A:B cis junction with the double bond exo to ring A. The stereochemistry of addition across the acetylene could be studied in only two cases. The disubstituted γ-ethynyl compound **1c** gave a mixture of syn and anti addition in the ratio of 58(±3):42(±3). With the terminal 6,6-dimethyl derivative **5e** the estimation was less accurate but syn addition was not less than 80% and may be higher. The incoming hydrogen comes in syn in spite of the fact that, in the final product, it is under considerable steric compression.

Any mechanism that seeks to explain the transformation of an acetylene ketone to an allyloxy anion has to consider the sequence of addition of two electrons and a proton or one electron and a hydrogen atom. The species produced at each stage, particularly the ones prior to and following the C–C

bond formation, have to be identified. In an aprotic medium proton abstraction is restricted to the relatively nonacidic solvent and to the substrate itself. The mechanism under these conditions need not be the same as the mechanism in liquid ammonia. Observation of the same stereoselectivity does imply some similarities, but, because of the doubt, data from liquid ammonia studies are used here only in a supplementary sense.

It is possible to cut across many possibilities because the result of reaction of **1c** strongly favors the intermediacy of a cyclized vinyl radical. The formation of substantial amounts of both isomers **18a** and **18b** from **1c** taken in conjunction with the shift towards syn addition observed with **5e** is best accounted for in terms of the equilibrium shown in Scheme V.[16]

Scheme V



Equilibration is expected to be almost complete because of the temperature[17] and the mode of addition. Conversion of the two vinyl radicals to the corresponding carbanions followed by protonation by solvent accounts for the products. Since vinyl carbanions are not expected to equilibrate under the reaction conditions[16b] the ratio of the isomeric carbanions is expected to be retained in the protonated product in spite of the considerable steric compression under which the newly introduced proton finds itself in one of the isomers.

The cyclized vinyl radical contains only one electron more than the substrate. Hence, cyclization must occur after one electron has been transferred to the acetylenic ketone. Since electron transfers are often reversible, the question arises as to whether the cyclization step is also reversible and that only the vinyl carbanion formation and protonation is irreversible. This point was settled by the formation of A:B cis compound exclusively in the reaction of **25**. By analogy with 4-keto steroids,[18] the A:B trans isomer of **26** should be stable relative to **26** and hence reversibility at the cyclization stage should have yielded at least some trans compound. In *A*-nor sterols the cis junction is more stable. However, since the environment of the ketone in **1a, 1b, 1c,** and **25** is identical, it is reasonable to conclude that kinetic control is operating in all cases leading to a 5β-ol derivative.

The distinctly different compounds isolated in the reaction of **25** and **1c** form the basis of another useful conclusion. Allenes are not being formed in spite of the strong base present.[19] The above two compounds should give the same allene. If this had occurred, then either starting material recovered or products formed in one set should have been contaminated with the other set. This did not happen nor was any allene detected.

It follows that *either* the acetylene *or* the ketone receives an electron (or alkali metal atom) from the reagent and the resulting radical ion attacks the other uncharged functional group. For the reductive cyclizations using metal and liquid ammonia, Stork has tentatively proposed that the acetylene radical ion is formed followed by nucleophilic attack on the ketone. Lansbury has questioned this interpretation[20] and believes that a nucleophilic attack on the acetylene by the radical ion formed from the ketone is more probable. The latter explanation requires that exclusive anti addition should take place across the acetylene.[21] The data for the aprotic cyclization are contrary to this expectation.

The crucial consideration is whether there is a substantial preference for electron transfer to one of the two functional groups. Preferential attack on the ketone would be expected from reduction potentials.[22] However, in solution, such considerations may not be entirely valid in view of the observations reported in an excellent paper on reduction of acetylenes by House.[17] Formation of species such as –C(Na)=C– is easier than would be anticipated on the basis of reduction potentials. Both ketones and isolated acetylenes (but not acetylides) are reduced by the blue solutions of alkali metals in ammonia or in HMP.[17] Since the alkali metal naphthalenes are much less powerful reducing agents, it was hoped that with these, evidence of selectivity might be obtained. Several studies are reported in the literature on use of these reagents for reduction of diaryl and monoaryl acetylenes[23] but no studies on isolated acetylenes or ketones are reported[24] except for an interesting study on δ-keto esters.[25]

The question of whether the acetylene was capable of accepting an electron from naphthalene sodium in THF was resolved by attempting the reduction of the alcohol **23** and the ketal **24.** These consumed 1.0 ± 0.2 and 0.0 ± 0.2 mol of the reagent only and were quantitatively recovered.[26] The dialkyl acetylene was chosen because failure to reduce a terminal acetylene could have been ascribed to proton abstraction leading to an acetylide ion incapable of reduction. The possibility that carbanion formation by abstraction of a proton from the carbon adjacent to the above acetylene is also ruled out by the titration values as well as the total recovery.

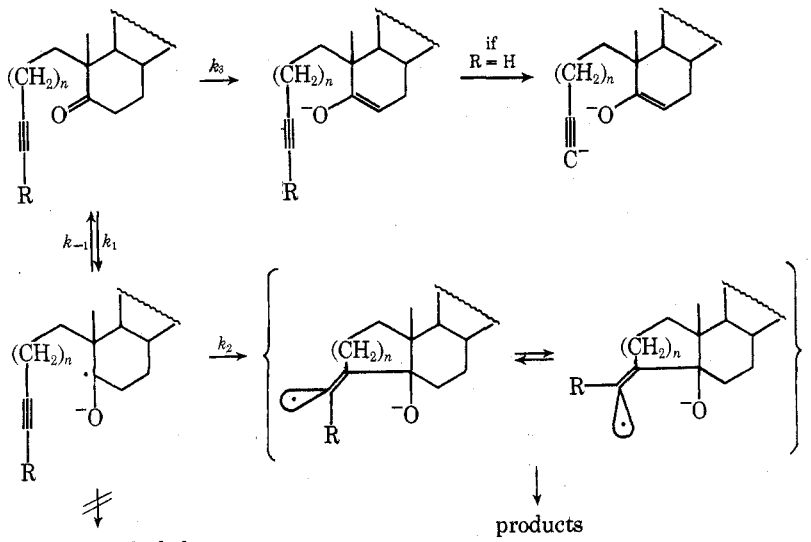
In contrast to the acetylene, the nonenolizable ketone **5a** reacts completely giving the reductively cyclized product **12** and the reduced alcohol **11.** The behavior of the enolizable ketones in **6** is illustrated by Scheme I which ascribes the apparent recovery of some of the ketones to enolate ion formation. It follows that none of the ketones escape attack by the reagent.

The conclusion that the ketone accepts electrons in preference taken in conjunction with the findings discussed below leads to the proposal given in Scheme VI.

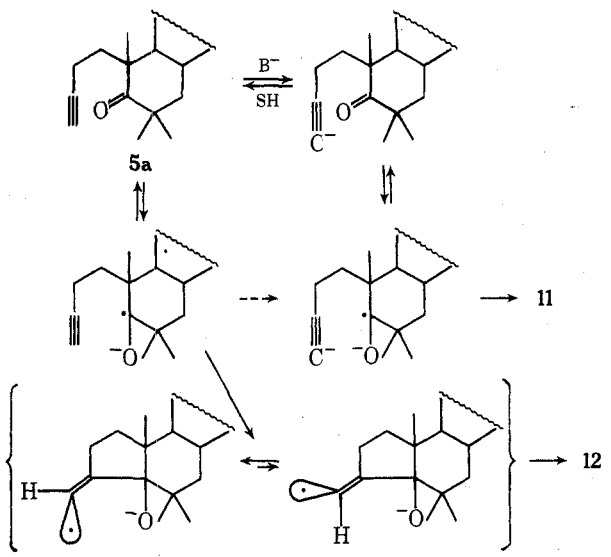
Here k_1 and k_3 represent rates of two simultaneous reactions between the same two reactants. Since both reactions involve the 5-keto group, the immediate environment of which is identical in **25, 1a,** and **1c,** the ratio k_1:k_3 would be expected to be nearly the same for these three compounds. In the event of k_1 representing a slow rate-determining step for product formation the ratio of product to recovery should have been the same for **25, 1a,** and **1c.** The actual ratios are, however, 8.2, 2.3, and 0.7, respectively. Thus the slow step in product formation must be k_2, which involves a C–C bond formation, with the ratios apparently reflecting the factors affecting the cyclization step. The equilibrium in the preceding step involves electron transfer. These are known to be fast and are certainly faster than proton abstraction.[27]

Scheme VII is an extension of Scheme VI to a hindered nonenolizable ketone. Only in this case is the uncyclized 5

Scheme VI



Scheme VII



hydroxy compound formed. This is accounted for by making the reasonable assumption that the rate of cyclization of the fully substituted hindered ketone is much less than in the nonhindered series. The rate of acetylide formation then becomes competitive. Radical cyclization at the acetylide ion is not expected. Hence the intermediate is diverted to the alcohol. This is borne out by deuteration studies. The deuterated **5e** in which the hydrogen attached to the sp carbon has been replaced by deuterium gives the undeuterated alcohol **11**. By the same token product **12** derived from this compound should have been 100% monodeuterated. However, 20–25% undeuterated compound was produced indicating that some reversal of acetylide formation must be occurring by proton abstraction from solvent.

In all the above cases a remarkable regiospecificity was observed. The exo olefins were formed exclusively. Intramolecular radical attack on acetylenes to give exclusively exo products has been reported.[28] A possible explanation for the observed regiospecificity may be that the transition state for cyclization may resemble starting material. Overlap of the orbital at C-5 with a p orbital on one of the sp carbons could lead to an incipient ring. In the larger of the two possible incipient rings the other sp carbon has to be accommodated within the ring whereas in the smaller incipient ring the sp carbon would be outside. Hence sufficient energy differences should exist so that the endo olefins, in six- or seven-membered rings, do not form in competition with the exo olefins.[29]

One interesting aspect of the mechanism is that, except for dimerization and reduction to dianion, there are no proven analogies for radical trapping of a radical ion. Because of this, the possibility that protonation at the oxygen precedes cyclization was considered. Proton abstraction from the substrate cannot account for the yield of 89% in the cyclization of **25** and the amount of naphthalene sodium consumed. So proton abstraction from solvent was the remaining possibility. A test of this was required under similar conditions. Assuming that the anion of cholesterol would be a stronger base than the above radical ion,[27] cholesterol was treated with $C_{10}H_8M$ under the conditions of the above experiments and excess methyl iodide was added subsequently. The amount of cholesteryl methyl ether produced indicated the minimum amount of alcohol that failed to abstract proton from the solvent. This was concentration, solvent, and counterion dependent. The results are given in Table II. Proton abstraction is very little with $C_{10}H_8K$ in DME. Yet yields in cyclization are quite high as seen in Table I. Hence prior protonation does not appear to be a condition for cyclization.[30]

Whereas a satisfactory picture has emerged about the mechanism of the reductive cyclization, the same is not true about the effect of solvent and counterion on this reaction which is summarized in Table I. The limited data can only be amenable to a highly speculative interpretation. A plausible one, conductive to further testing, is herein offered. The slight superiority of THF over DME could be due to the encroachment of proton catalyzed cyclization occurring to a small extent in the former but not the latter, the proton being provided by the solvent. Data in Table II show that this occurs more readily in THF than DME. The significant drop in yields of cyclization with naphthalene lithium solutions as compared to sodium and potassium ones could be due to the former being superior at proton abstraction thereby giving an increased rate of enolate ion formation and hence more recovery of starting material. Naphthalene lithium is in fact preferred over the others for a number of reactions involving proton abstraction from carbon.[31] The actual species involved is not

Table II. Variations in Yield of Methyl Ether of Cholesterol[a]

Reagent	$Li^+Nap\cdot^-$, THF		$Li^+Nap\cdot^-$, DME		$Na^+Nap\cdot^-$, THF		$Na^+Nap\cdot^-$, DME		$K^+Nap\cdot^-$, THF		$K^+Nap\cdot^-$, DME	
Normality	0.60	0.35	0.70	0.41	0.70	0.40	0.75	0.45	0.71	0.50	0.78	0.56
% ether[b]	38	30	83	59	43	33	91	78	58	45	96	89

[a] Cholesterol was titrated with $C_{10}H_8M$ in DME/THF and after decolorization, excess methyl iodide was added. [b] This value is based on cholesteryl methyl ether isolated by column chromatography. The other component was cholesterol. Total material accounted for was 95 ± 3%.

Table III. Catalytic Effect of Naphthalene on Reaction of Sodium[a] with 1a in THF/DME

Solvent	Catalyst[b]	2a	3a	1a	Solvent	Catalyst[b]	2a	3a	1a
THF	0.0 mol	38[c]	6	50	DME	0.0 mol	43[c]	8	41
THF	0.2 mol	72		23	DME	0.2 mol	83		11
THF	0.4 mol	80		15	DME	0.4 mol	90		6

[a] Slow reaction, time 5.5 h. [b] Moles of catalyst relative to 1 mol of **1a**. [c] Percentage yields.

known but the dianion formed by disproportionation of $C_{10}H_8Li$ is a strong candidate.

Experimental Section

General. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer. Uv spectra were recorded on a Beckman DB spectrophotometer. NMR spectra were obtained with a Varian A-60 spectrometer in CCl_4 or $CDCl_3$ with Me_4Si as internal standard. Optical rotations were determined in chloroform at room temperature with a Carl-Zeiss Winkel spectropolarimeter. Melting points were determined on a standard melting point apparatus and are uncorrected. THF or DME were purified for all purposes by refluxing initially with sodium or with KOH and alumina followed by another distillation from $C_{10}H_8Na$. In all cases, standard grade alumina was used for chromatographic separation unless otherwise stated.

All reactions as well as column chromatography were followed by TLC using microslides with detection by exposure to iodine vapors. 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 till neutral and dried over anhydrous sodium sulfate.

Preparation and Estimation of Naphthalene Sodium. In a thoroughly cleaned and dry 250-ml two-necked flask was taken 100 ml of freshly purified THF or DME. This was stirred magnetically and 9.6 g (75 mmol) of freshly crystallized and dried naphthalene was added under nitrogen atmosphere. Freshly cut sodium (2.9 g, 130 mmol) was added to this solution in relatively small pieces maintaining throughout a positive nitrogen atmosphere. The solution became green in about 15 min and stirring continued for 3 h thereafter. A narrow-mouthed bent glass tube connected with a buret was then inserted below the surface of the reagent. The buret was flushed with nitrogen and kept under nitrogen atmosphere and could be filled with the reagent by application of greater pressure of nitrogen on the surface of the reagent in the flask. Titrations and reactions were carried out by addition under nitrogen atmosphere to a magnetically stirred solution of sterol. This reagent was estimated by addition to a solution of 386 mg (1 mmol) of cholesterol in 4 ml of THF till the solution became faint green. It was observed that 1.6 ml of the reagent was consumed indicating that a 0.6 N solution had been obtained. This was found to be reproducible over several experiments. Exactly identical procedure was followed for preparing $C_{10}H_8Li$ and $C_{10}H_8K$.

The following experiment describes in detail the use of this reagent for reductive cyclization. The same procedure was followed for all other reductive cyclizations, the only difference being that excess methyl iodide was added prior to workup when trapping of the enolate was desired.

Reductive Cyclization of 4,5-Secocholest-3-yn-5-one (1a) with Naphthalene Sodium. Solution of naphthalene sodium was added under nitrogen atmosphere to a well-stirred solution of 384 mg (1 mmol) of **1a** in 5 ml of THF at room temperature till a faint green end point. It was found that 2.1 mmol of the reagent was required. The faint color discharged by itself in about 10 min after turning off nitrogen. The reaction mixture was worked up in the usual way and chromatographed on alumina. Sufficient pentane was used to elute all the naphthalene. Use of benzene/pentane gave 104 mg of the unreacted material followed by 263 mg of 3-methylene-*A*-norcholestan-5β-ol (**2a**). On crystallization from aqueous methanol this had mp 57–58°; $[\alpha]D$ +20° (*c* 0.12) (lit.[2] mp 58°, $[\alpha]D$ +20°). It was identical with an authentic sample in its ir and NMR.

The yields of **2a** were not noticeably affected by reversing the mode of addition or by lowering the temperature to 0 °C.

The reductive cyclization of **1a** was carried out in an identical fashion using DME as solvent. The result of this experiment as well as those with $C_{10}H_8K$ and $C_{10}H_8Li$ in THF and DME are given in Table I.

Reductive Cyclization of 1a with Na in THF/DME with and without Naphthalene. To 384 mg (1 mmol) of **1a** in 8 ml of THF or DME 92 mg (4 mg-atoms) of Na metal and specific amounts of naphthalene were added and stirred at room temperature for 5.5 h under a nitrogen atmosphere. No green color was observed throughout the experiment except for a faint green color on the metal surface. The solution was then filtered to remove sodium and washed with dry ether and from the combined filtrates solvent was removed under vacuum to leave a residue which was chromatographed. The results are given in Table III. The yields of **1a**, **2a**, and **3a** are based on the actual weights of the compounds obtained on chromatography.

Naphthalene Sodium/Methyl Iodide on 1a (Trapping of Enolate Ion). A stirred solution of 384 mg (1 mmol) of **1a** in 5 ml of DME was titrated to a faint green end point with a DME solution of naphthalene sodium and immediately 0.08 ml (1.3 mmol) of methyl iodide in 4 ml of DME was added and the mixture stirred for 10 min. It was then poured into water and extracted with ether after neutralizing. The ether extract was washed with sodium thiosulfate solution and then with water and finally dried over anhydrous sodium sulfate. Removal of ether under vacuum and chromatography as usual gave 128 mg of an oily material which was formulated as 6α,6β-dimethyl-4,5-secocholest-3-yn-5-one (**5a**). It has $[\alpha]D$ −3° (*c* 0.13); ir (CCl_4) 3305 (≡CH), 2110 (–C≡C–), 1690 cm^{-1} (C=O); NMR (CCl_4) δ 0.76 (3 H, s, C-18 methyl), 1.03, 1.04, and 1.06 (C-19 and C-6 methyls). Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.13; H, 11.43.

This was followed by 235 mg of cyclized alcohol **2a**.

Similar results were obtained when DME was replaced by THF. Disubstitution at the 6 position was confirmed by NMR of 11 and its acetate in both of which the C-5 H is a singlet.

6α,6β-Dimethyl-4,5-secocholest-3-yn-5ε-ol (11). To a solution of 410 mg (1 mmol) of acetylenic ketone **5a** in 8 ml of methanol was added 185 mg (5 mmol) of $NaBH_4$ in one portion. The reduction was complete in about 4 h; 10% acetic acid was added dropwise till the solution became slightly acidic. This was then extracted with ether and washed with a solution of sodium bicarbonate and then with water. The ether was dried over anhydrous sodium sulfate and then distilled off under vacuum to yield a thick mass which was chromatographed on alumina. Elution with 1:1 hexane–benzene gave 20 mg of an oil. It had $[\alpha]D$ +2° (*c* 0.11); ir (CCl_4) 3590 (OH), 3310 (≡CH), 2120 cm^{-1} (C≡C). It was not further characterized.

Further elution gave 350 mg of the crystalline 6α,6β-dimethyl-4,5-secocholest-3-yn-5ε-ol (**11**). This had mp 76–77 °C when crystallized from methanol: $[\alpha]D$ +4° (*c* 0.13); ir (CCl_4) 3580 (OH), 3310 (≡CH), 2120 cm^{-1} (C≡C); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 0.93 (9 H, s, C-19 and C-6 methyls), 3.08 (1 H, s, C-5 H). Anal. Calcd for $C_{29}H_{50}O$: C, 84.07; H, 12.08. Found: C, 83.87; H, 12.26.

Reduction with $LiAlH_4$ in ether gave the same compound.

Acetylation of **11** with acetic anhydride in refluxing pyridine gave the corresponding acetate in quantitative yield. It had mp 68 °C; $[\alpha]D$ −20° (*c* 0.12); ir (CCl_4) 3400 (≡CH), 2150 (C≡C), 1770 cm^{-1} (C=O); NMR (CCl_4) δ 0.73 (3 H, s, C-18 methyl), 0.96 (9 H, s, C-19 and C-6 methyls), 2.10 (3 H, s, $-OCOCH_3$), 4.5 (1 H, s, C-5 H). Anal. Calcd for $C_{31}H_{52}O_2$: C, 82.50; H, 11.40. Found: C, 82.27; H, 11.21.

Oxidation of 412 mg of **11** with CrO_3 and pyridine in CH_2Cl_2 overnight at room temperature gave 350 mg of **5a**.

Naphthalene Sodium on 17β-Hydroxy-4,5-secoandrost-3-yn-5-one (1b). Following the literature[2] procedure **1b** was synthesized and 288 mg of it was treated with naphthalene sodium as described above. Chromatography yielded 260 mg of a mixture of **1b** and **2b** as judged by ir and NMR. Various attempts to separate the mixture failed. The mixture could be estimated to contain 55% **2b** by NMR.

Naphthalene Sodium/Methyl Iodide on 17β-Hydroxy-4,5-secoandrost-3-yn-5-one (1b). Titration of a solution of 288 mg (1 mmol) of **1b** in 5 ml of DME followed by addition of 0.25 ml (4 mmol) of methyl iodide after workup and chromatography gave 117 mg of 6α,6β-dimethyl-17β-methoxy-4,5-secoandrost-3-yn-5-one (**5c**). It had $[\alpha]D$ −3° (*c* 0.10); ir (CCl_4) 3305 (≡CH), 2120 (C≡C), 1692 (C=O), 1450, 1385, 1370, 1100, 1030 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.0, 1.03, and 1.08 (C-19 and C-6 methyls), 3.28 (3 H, s, $-OCH_3$). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.15; H, 10.12.

Further elution with benzene–pentane gave 139 mg of crystalline 3-methylene-17β-methoxy-*A*-norandrostan-5β-ol (**2c**). It had mp 151–152 °C when crystallized from methanol; $[\alpha]D$ + 21° (*c* 0.12); ir (CCl_4) 3580 (OH), 890 cm^{-1} (=CH_2); NMR (CCl_4) δ 3.25 (3 H, s, $-OCH_3$), 4.98 (2 H, m, =CH_2). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.94; H, 10.51. Found: C, 78.80; H, 10.40.

Preparation of 4,5-Secoandrost-3-yne-5,17-dione (6). To a stirred solution of 4 ml of pyridine in CH_2Cl_2 was added 400 mg of chromium trioxide. To this 400 mg of **1b** in 5 ml of CH_2Cl_2 was added and left overnight. The reaction mixture was worked up to yield after chromatography 380 mg of 4,5-secoandrost-3-yne-5,17-dione (**6**). It had mp 118–120 °C; ir (Nujol) 3315 (≡CH), 2125 (C≡C), 1740 and 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.89 (3 H, s, C-18 methyl), 1.10 (3 H, s, C-19 methyl). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.92; H, 8.87.

Naphthalene Sodium on 4,5-Secoandrost-3-yne-5,17-dione (6). A solution of 286 mg (1 mmol) of acetylenic diketone **6** in 4 ml of THF was titrated with naphthalene sodium in THF. Workup and chromatography on alumina gave 65 mg of the unreacted starting material, followed by 130 mg of 3-methylene-*A*-norandrostan-5β-ol-17-one (**7a**). It had $[\alpha]D$ +20° (*c* 0.11); ir (CCl_4) 3550 (OH), 1740 (C=O), 900 cm^{-1} (=CH_2). The last fraction gave 68 mg of the cyclized diol **2b**. It had mp 188 °C; $[\alpha]D$ +22° (*c* 0.13) [lit.[2] mp 188–189 °C, $[\alpha]D$ +22° (*c* 0.12)], and had ir and NMR identical with that of an authentic sample.

Sodium borohydride reduction of **7a** gave **2b**.

Naphthalene Sodium on 6α,6β-Dimethyl-4,5-secocholest-3-yn-5-one (5a). Preformed naphthalene sodium in DME was added to 205 mg (0.5 mmol) of the above acetylenic ketone **5a** in 3 ml of DME till a faint green end point. By estimation, it was found that 0.9 mmol of the reagent was consumed. The reaction mixture was worked up as usual and chromatographed on alumina. Elution with pentane, after removal of naphthalene, gave 123 mg of 3-methylene-6α,6β-dimethyl-*A*-norcholestan-5β-ol (**12**). It was crystallized from aqueous methanol. It had mp 49–51 °C; $[\alpha]D$ +8° (*c* 0.14); ir (CCl_4) 3610 (OH), 900 cm^{-1} (=CH_2); NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 1.06, 1.13 (C-19 and C-6 methyls), 4.98 (1 H, s), and 5.25 (1 H, s) (=CH_2). Anal. Calcd for $C_{29}H_{50}O$; C, 84.07; H, 12.08. Found: C, 83.97; H, 11.90.

Further elution gave 79 mg of **11** identical in all respects with the borohydride reduction product reported earlier.

Similar experiments with naphthalene sodium in THF added to 410 mg (1 mmol) of **5a** in 5 ml of THF gave after workup and chromatography 238 mg of **12** and 162 mg of **11**.

For the sake of comparison, the reductive cyclization of **5a** was attempted by the liquid ammonia procedure. A solution of 410 mg (1 mmol) of the dimethyl acetylenic ketone **5a** in 8 ml of THF was added to 20 ml of liquid ammonia. To the stirred mixture was added 69 mg (3 mg-atoms) of freshly cut sodium, followed by 1.5 ml of dry *t*-BuOH. After 6 min, the reaction was quenched by adding methanol. Ammonia was evaporated and the ether soluble portion was chromatographed on silica gel. Elution with hexane gave 370 mg of an oil. It had NMR ($CDCl_3$) δ 0.73 (3 H, s, C-18 methyl), 1.03, 1.1, 1.26 (C-19 and C-6 methyls), 1.78 (3 H, s, C-3 methyl). On the spectral evidence it is tentatively formulated as 3,6α,6β-trimethyl-*A*-norcholest-3-ene (**13**).

3,6α,6β-Trimethyl-*A*-norcholesta-1,3-diene (14). To a solution of 207 mg of 6α,6β-dimethyl tertiary alcohol **12** in 20 ml of acetone was added 28 mg of *p*-toluenesulfonic acid and the mixture was stirred under nitrogen atmosphere. The starting material completely disappeared in about 30 min. Workup and chromatography over alumina gave 185 mg of 3,6α,6β-trimethyl-*A*-norcholesta-1,3-diene (**14**). It was crystallized from chloroform–methanol and had mp 76–77 °C; $[\alpha]D$ 0°; uv λ_{max} (EtOH) 245 nm (ε 3800); ir (CCl_4) 2860, 1460, 1380, 1360 cm^{-1}; NMR (CCl_4) δ 0.66 (3 H, s, C-18 methyl), 0.80, 1.04, 1.16 (C-19 and C-6 methyls), 2.0 (3 H, s, C-3 methyl), 5.9 and 6.1 (2 H, AB q, *J* = 5.5 Hz). Anal. Calcd for $C_{29}H_{48}$: C, 87.88; H, 12.12. Found: C, 87.49, H, 11.90.

β-Epoxide of 3-Methylene-6α,6β-dimethyl-*A*-norcholestan-5β-ol (15 from 12). To 206 mg of the tertiary allylic alcohol **12** was added 10 ml of 0.77 N perbenzoic acid in chloroform and the mixture was kept overnight at 5 °C. The solution was extracted with $CHCl_3$ after dilution with water and washed with solutions of potassium iodide, sodium thiosulfate, sodium bicarbonate, and finally water. The $CHCl_3$ extract was dried by passing over anhydrous sodium sulfate and concentrated in vacuo. Crystallization from aqueous acetone gave 120 mg of the epoxide **15**. It had mp 163–164 °C; $[\alpha]D$ +4° (*c* 0.13); ir (CCl_4) 3590 (OH), 1465, 1380, 912 cm^{-1}; NMR (CCl_4) δ 0.73 (3 H, s, C-18 methyl), 1.04 (9 H, s, C-19 and C-6 methyls), 2.75 and 3.48 (2 H, AB q, *J* = 5 Hz). Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.93; H, 11.62. Found: C, 80.68; H, 11.40.

Another crop (45 mg) of **15** was obtained from the mother liquor.

3α,6α,6β-Trimethyl-*A*-norcholestane-3β,5β-diol (16). To a solution of 215 mg of the epoxy alcohol **15** in 20 ml of dry ether was added 500 mg of $LiAlH_4$ and the mixture was refluxed for 3 h. A saturated solution of aqueous sodium potassium tartarate was added slowly and the product was ether extracted. Removal of ether under vacuum gave 150 mg of an oily material which was crystallized from aqueous methanol. It was formulated as 3α,6α,6β-trimethyl-*A*-norcholestane-3β,5β-diol (**16**). It had mp 95 °C; $[\alpha]D$ +13° (*c* 0.14); ir (CCl_4) 3510 (OH), 1460, 1380, 1090, 1030 cm^{-1}; NMR (CCl_4) δ 0.74 (3 H, s, C-18 methyl), 1.06, 1.11 (C-19 and C-6 methyls), 1.6 (3 H, s, C-3 methyl). Anal. Calcd for $C_{29}H_{52}O_2$: C, 80.56; H, 12.04. Found: C, 80.21; H, 11.71.

5α,6α,6β-Trimethyl-*A*-norcholestan-3-one (17). To 216 mg of the diol **16** was added 16 ml of 5% methanolic HCl and the mixture was refluxed for about 15 min. The reaction mixture was cooled, neutralized by adding dilute bicarbonate solution, and extracted with ether. Ether was removed under vacuum and the resulting residue chromatographed on alumina. Elution with 1:1 hexane–benzene gave 165 mg of 5α,6α,6β-trimethyl-*A*-norcholestan-3-one (**17**). Crystallization from aqueous methanol gave mp 68–70 °C; $[\alpha]D$ −43° (*c* 0.10); ir (CCl_4) 1760 cm^{-1} (C=O); NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 1.08, 1.10 (C-19, C-5, and C-6 methyls); $[\alpha]_{365}$ −306°, $[\alpha]_{436}$ −125°, $[\alpha]_{546}$ −58°, $[\alpha]_{578}$ −49°, $[\alpha]_{589}$ −45°. Anal. Calcd for $C_{29}H_{50}O$: 83.99; H, 12.15. Found: C, 83.68; H, 12.00.

Deuterium Exchange on 6α,6β-Dimethyl-4,5-secocholest-3-yn-5-one. A solution of 412 mg of dimethyl acetylenic ketone **5a** in NaOD–D_2O (prepared by adding a few pieces of sodium to D_2O) was refluxed on a water bath, using 5 ml of THF as solvent, under a positive nitrogen atmosphere for 0.5 h. The reaction mixture was worked up by petroleum ether extractions followed by washings with D_2O. The petroleum ether solution was passed through a fine filter to get a clear solution which was then concentrated and dried. By repeating the process a couple of times, complete deuterium exchange, as determined by disappearance of ir absorption at 3310 cm (≡CH), was achieved to give 390 mg of **5e**: ir (CCl_4) 2590 (≡CD), 2125 (C≡C), 1690 cm^{-1} (C=O).

Naphthalene Sodium on Monodeuterated Acetylenic Ketone (5e). A solution of preformed naphthalene sodium in THF was added to a solution of 413 mg of monodeuterated acetylenic ketone **5e** in 5 ml of THF till a faint green end point. The color was allowed to discharge by itself after which the reaction mixture was worked up by extractions with petroleum ether (bp 40–60 °C) followed by D_2O washings. Petroleum ether was concentrated in vacuo and chromatographed over silica gel. Elution with pentane gave initially 240 mg of the reductively cyclized product. Later fractions gave 162 mg of 6α,6β-dimethyl-4,5-secocholest-3-yn-5ε-ol (**11**) which had ir (CCl_4) 3590 (OH), 3310 (≡CH), 2120 cm^{-1} (C≡C). The peak at 2590 cm^{-1} (≡CD) was completely absent. Its NMR was identical with that of undeuterated **11** showing that the 5α-H had not been replaced by deuterium.

The reductively cyclized product, on the other hand, contained considerable monodeuterated compound accompanying some undeuterated material. A careful comparison by NMR of the areas under the curve with the undeuterated **12** at the vinylic position indicated

that the singlet at δ 5.25 integrated for 0.8–1.0 protons and the relative areas at δ 5.25: 4.98 were 4:1.

4-Methyl-4,5-secocholest-3-yn-5-one (1c). 4-Methylcholest-4-en-3-one was prepared from cholestenone by treating with potassium *tert*-butoxide and methyl iodide in *tert*-butyl alcohol.[35] This was then epoxidized by addition of 30% H_2O_2 at a pH of about 12. The resulting 4,5-epoxy-4-methylcholestan-3-one was converted to **1c** as follows. To a solution of 1 g (2.5 mmol) of the above epoxy ketone in 250 ml of ethanol was added a solution of 470 mg of tosylhydrazine in 50 ml of ethanol. The reaction mixture was refluxed for 3–4 h. The alcohol was removed under vacuum and the resulting brown residue extracted with ether. The ether layer was washed with a solution of sodium bicarbonate, followed by water washings and dried over anhydrous sodium sulfate. Removal of ether gave a brown, gummy mass which was chromatographed over alumina. Elution with 1:1 hexane–benzene gave 650 mg of methyl acetylenic ketone **1c.** It was an oil and had [α]D +29° (*c* 0.12); ir (CCl_4) 2120 (C≡C), 1700 (C=O), 1460, 1365, 1265, 1070, 970, 940 cm^{-1}; NMR (CCl_4) δ 0.76 (3 H, s, C-18 methyl), 1.08 (3 H, s, C-19 methyl), 1.65 (3 H, s, $-C{\equiv}C-CH_3$). Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.02; H, 11.29.

Naphthalene Sodium on 4-Methyl-4,5-secocholest-3-yn-5-one (1c). A solution of 398 mg of 4-methyl-4,5-secocholest-3-yn-5-one in 5 ml of THF was titrated with naphthalene sodium in THF till a faint green color developed. The reaction mixture was worked up as usual, chromatographed on alumina, and eluted with pentane to remove all the naphthalene. Increasing the polarity by taking 10% benzene in pentane gave 220 mg of the unreacted starting material **1c** followed by 160 mg of the more polar mixture of stereoisomeric 3-ethylidene-*A*-norcholestan-5β-ols (**18a + 18b**). This mixture could not be separated and had [α]D +28 °C (*c* 0.13); ir (CCl_4) 3500 (OH), 1450, 1375, 1020, 978, 935, 912, 885 cm^{-1}. Anal. Calcd for $C_{28}H_{48}O$: C, 83.90; H, 12.07. Found: C, 83.56; H, 12.41.

Naphthalene Sodium/Methyl Iodide on 4-Methyl-4,5-secocholest-3-yn-5-one (1c). A solution of naphthalene sodium in DME was added to a well-stirred solution of 398 mg (1 mmol) of acetylenic ketone **1c** in 5 ml of DME till a faint green end point, and immediately 0.09 ml (1.3 mmol) of methyl iodide was added. The reaction mixture was stirred for the next 10 min, poured into water, neutralized, and ether extracted. The ether solution was then washed with a solution of sodium thiosulfate and finally with water. Removal of ether gave a gum which was chromatographed over silica gel and eluted with 1:1 hexane–benzene. Initial fractions gave 210 mg of 4,6α,6β-trimethyl-4,5-secocholest-3-yn-5-one (**5d**). It had [α]D −2° (*c* 0.14); ir (CCl_4) 2120 (C≡C), 1695 (C=O), 1580 cm^{-1}; NMR (CCl_4) δ 0.68 (3 H, s, C-18 methyl), 1.0, 1.15 (C-19 and C-6 methyls), 1.76 (3 H, s, $-C{\equiv}C-CH_3$). Anal. Calcd for $C_{30}H_{50}O$: C, 84.45; H, 11.81. Found: C, 84.19; H, 11.60.

Later fractions gave 160 mg of the cyclized compounds **18a** and **18b.**

Conversion of the Cyclized Tertiary Alcohols (18a and 18b) to Ketone (19). To a solution of 190 mg (0.5 mmol) of tertiary allylic alcohol (**18a** and **18b**) in 20 ml of acetone containing 2–3 drops of water was added a solution of 2 mg of *p*-toluenesulfonic acid in 2 ml of acetone with constant stirring under nitrogen atmosphere. After 1 h the reaction mixture was worked up and chromatographed over alumina. Elution with benzene gave initially an isomeric alcohol which had [α]D +55° (*c* 0.10). Later fractions gave the other isomeric alcohol which had [α]D +41° (*c* 0.11).

To a stirred solution of 1 ml of pyridine in CH_2Cl_2 was added 100 mg (1 mmol) of chromium trioxide. To this 100 mg (0.25 mmol) of the isomeric alcohol, [α]D +55°, in 5 ml of CH_2Cl_2 was added and left overnight. The reaction mixture was worked up as described elsewhere and chromatographed on alumina. Elution with benzene gave 60 mg of ketone **19.** It was crystallized from methanol–acetone and had mp 93–95 °C; [α]D +98° (*c* 0.12); uv λ_{max} (EtOH) 257 nm (ε 15 000); ir (CCl_4) 1700 (C=O), 1610 cm^{-1} (C=C); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.01 (C-19 methyl), 2.04 (3 H, s, $-COCH_3$) shows no vinyl hydrogen. Anal. Calcd for $C_{28}H_{46}O{\cdot}CH_3OH$: C, 81.45; H, 11.08. Found: C, 81.58; H, 11.34.

Similar oxidation of the alcohol, [α]D +41°, gave the same ketone (**19**).

β-Epoxides of 18a and 18b. To 180 mg of the stereoisomeric allylic alcohols (**18a** and **18b**) was added 8 ml of 0.77 N perbenzoic acid in chloroform and the mixture was left overnight at 5 °C. It was worked up as described earlier and chromatographed over alumina. Elution with benzene gave initially 68 mg of **21** which crystallized readily from methanol. It had mp 108–110 °C; [α]D +11° (*c* 0.11); ir (KBr) 3400, 2880, 1450, 1370, 1025 cm^{-1}; NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 0.97 (C-19 methyl), 1.5 (3 H, d, *J* = 6 Hz), and 3.11 (1 H, q, *J* = 6 Hz)[$-CH(O)CH_3$]. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.47; H, 11.35.

Later fractions gave 92 mg of **20** which was crystallized from methanol. It had mp 96–98 °C [α]D +10° (*c* 0.13); ir (KBr) 3390, 2880, 1450, 1370, 1025 cm^{-1}; NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.01 (3 H, s, C-19 methyl), 1.28 (3 H, d, *J* = 6 Hz), and 3.11 (1 H, q, *J* = 6 Hz) [$-CH(O)CH_3$]. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.79; H, 11.39.

3α-Ethyl-*A*-norcholestane-3β,5β-diol (22). To a solution of 104 mg (0.25 mmol) of the epoxy tertiary alcohol **20** in 50 ml of dry ether was added 400 mg of $LiAlH_4$ and the mixture was refluxed for 3 h. After the addition of aqueous sodium potassium tartrate, the product was extracted with ether, dried, and concentrated under vacuum to yield a residue which was chromatographed over alumina. Elution with 1:1 benzene–ether gave 80 mg of the diol **22.** On crystallization from methanol, it had mp 113–114 °C; [α]D −6° (*c* 0.13); ir (KBr) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.65 (3 H, s, C-18 methyl) and 1.0 (C-19 methyl). [The corresponding 3α-methyl-*A*-norcholestane-3β,5β-diol has NMR ($CDCl_3$) δ 0.65 (C-18 methyl) and 1.00 (C-19 methyl)].[2] Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.03. Found: C, 80.15; H, 11.87.

Reduction of **21** under the above conditions gave the same diol **22** as confirmed by identity of melting point, [α]D, ir, and NMR.

4-Methyl-4,5-secocholest-3-yn-5α- and -5β-ols and 5-Ketal (24) from 1c. To a solution of 396 mg (1 mmol) of methyl acetylenic ketone **1c** in 20 ml of methanol was added 111 mg (3 mmol) of sodium borohydride in one portion. The reaction mixture was worked up as described earlier and chromatographed over alumina. Elution with 1:1 hexane–benzene gave 160 mg of 4-methyl-4,5-secocholest-3-yn-5α-ol. It had mp 87–88 °C; [α]D +32°.

Later elutions gave 210 mg of 4-methyl-4,5-secocholest-3-yn-5β-ol (**23**). It had mp 78–80 °C; [α]D +12° (*c* 0.12). (The configurations of these compounds have been tentatively assigned on the basis of their rotations.)

To a solution of 990 mg (2.5 mmol) of **1c** in 50 ml of dry benzene was added 50 mg of *p*-toluenesulfonic acid and 248 mg (4 mmol) of ethylene glycol. The flask was attached to a Dean-Stark unit and water was azeotroped out. Workup and chromatography gave 740 mg of 4-methyl-4,5-secocholest-3-yne-5-ketal (**24**).

Naphthalene Sodium on 23 and 24. A solution of naphthalene sodium in THF was added to a solution of 398 mg (1 mmol) of **23** in 5 ml of THF till a faint green end point. By estimation, it was found that 1.0 mmol of the reagent was consumed. Workup and chromatography as in earlier experiments gave 388 mg of starting material **23.**

Addition of 3 mmol of the reagent to 398 mg (1 mmol) of **23** and stirring for 25 min gave after workup and chromatography 390 mg of the starting material **23.**

A solution of naphthalene sodium in THF was added to a solution of 104 mg (0.25 mmol) of the ketal **24** in 3 ml of THF till a faint green end point. It took up 0.1 mmol of the reagent. Workup and chromatography gave 100 mg of the starting material **24.** Repetition of the above experiment with 104 mg (0.25 mmol) of **24** by adding 0.5 mmol of the reagent and stirring for 25 min gave, after workup and chromatography, 101 mg of the starting ketal **24.**

4a,5-Seco-*A*-homocholest-4(4a)-yn-5-one (25). Sodamide[14] was prepared by bubbling ammonia into a solution of 0.6 N naphthalene sodium externally cooled in an ice bath till the color changed from green to greyish. This solution was practically free of sodium. Ammonia was then displaced by nitrogen and the resulting turbid solution was added in fivefold excess to a solution of 196 mg of methyl acetylenic ketone **1c** in 30 ml of dry toluene. The mixture was refluxed for 12 h and allowed to cool to room temperature. Aqueous HCl was added slowly to make it acidic and then the mixture was stirred for 20 min. The two layers were separated and the aqueous layer was saturated with brine solution and extracted with ether. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Removal of solvent and chromatography over alumina gave, after naphthalene, 280 mg of an oily mixture which was not identified.

Later elutions gave 30 mg of the isomerized acetylenic ketone **25** as shown by ir and by formation of Ag salt. Its constants are given below.

To obtain better yields of the isomerized ketone **25,** the above experiment was repeated with the ketal **24.** Sodamide prepared as described in the previous reaction was added in excess in a solution of 600 mg (1.4 mmol) of ketal **24** in 80 ml of dry toluene and refluxed for 12 h. Workup and chromatography as before gave 400 mg of the isomerized ketal. This ketal was dissolved in 5 ml of THF, treated with 10 ml of 10% H_2SO_4, and left overnight. Workup and chromatography gave 300 mg of 4a,5-seco-*A*-homocholest-4(4a)-yn-5-one (**25**) as an oil: ir (CCl_4) 3310 (≡CH), 2210 (C≡C), 1709 cm^{-1} (C=O); NMR (CCl_4) δ 0.75 (3 H, s, C-18 methyl), 1.08 (C-19 methyl). Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.10; H, 11.29.

4-Methylenecholestan-5β-ol (26). A solution of preformed naphthalene sodium in THF was added to a stirred solution of 198 mg (0.5 mmol) of the acetylenic ketone **25** in 3 ml of THF to a faint green end point. Approximately 2 mmol of the reagent was consumed per millimole of the starting material. Workup and chromatography over alumina and eluting with pentane gave 20 mg of the unreacted starting material **25**. Increasing the polarity of the eluent gave 160 mg of 4-methylenecholestan-5β-ol (**26**). It had $[\alpha]D$ +21° (*c* 0.11) but could not be crystallized: ir (CCl_4) 3510 (OH), 910 cm^{-1} (=CH_2); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.03 (C-19 methyl), 4.96 (2 H, m, =CH_2).

4α-Methylcholestane-4β,5β-diol (30) from 4-Methylcholest-3-en-5β-ol (28). To 100 mg (0.25 mmol) of the allylic alcohol **28**[15] was added 4 ml of 0.77 N perbenzoic acid in chloroform and the mixture was left overnight at 5 °C. Workup and crystallization from methanol gave 72 mg of the epoxide **29**. It had mp 113–114 °C; $[\alpha]D$ +46° (*c* 0.13); ir (KBr) 3340 (OH), 1030 cm^{-1}; NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 0.97 (C-19 methyl), 1.38 (3 H, s, C-4 methyl), 3.18 (1 H, broad s, C-3 H). Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.30; H, 11.70.

To a solution of 104 mg (0.25 mmol) of the epoxy alcohol **29** in 50 ml of dry ether was added 400 mg of $LiAlH_4$ and the mixture was refluxed for 3 hr. Workup and crystallization from methanol gave 70 mg of 4α-methylcholestane-4β,5β-diol (**30**). It had mp 163–164 °C; $[\alpha]D$ +8° (*c* 0.11); ir (KBr) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.65 (3 H, s, C-18 methyl), 0.98 (3 H, s, C-19 methyl), 1.45 (3 H, s, C-4 methyl). Anal. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.03. Found: C, 80.18; H, 11.67.

The same diol **30** was produced along with an isomer by treating 300 mg of 4-methylcholest-4-ene[3] (obtained by $LiAlH_4/AlCl_3$ reduction of 4-methylcholest-4-en-3-one) dissolved in 25 ml of ether with a solution of 300 mg of OsO_4 in 2.5 ml of pyridine and working up after 40 h.

Conversion of 26 via Epoxide 27 to Diol 30. To 100 mg (0.25 mmol) of the tertiary allylic alcohol **26** was added 4 ml of 0.77 N perbenzoic acid in chloroform and the mixture was left overnight at 5 °C. Workup and crystallization from aqueous methanol gave 72 mg of the corresponding epoxide **27**. It had mp 110–112 °C; $[\alpha]D$ +7° (*c* 0.12); ir (KBr) 3350 cm^{-1} (OH); NMR (CCl_4) δ 0.70 (3 H, s, C-18 methyl), 1.0 (C-19 methyl), 2.69 (1 H, d, J = 5 Hz), and 3.12 (1 H, d of d, J = 5 and 1.5 Hz) [–(O)CH_2]. Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.57; H, 11.72.

To a solution of 104 mg (0.25 mmol) of the above epoxy tertiary alcohol **27** in 50 ml of dry ether was added 400 mg of $LiAlH_4$ and the mixture was refluxed for 3 h. Workup of the reaction mixture followed by crystallization from methanol gave 70 mg of **30** identical in its melting point, $[\alpha]D$, ir, and NMR with that prepared in the previous experiment.

O-Methylation of Cholesterol with Methyl Iodide and Naphthalene Sodium. A solution of naphthalene sodium in DME was added to a stirred solution of 386 mg (1 mmol) of cholesterol in 5 ml of DME to a faint green end point, followed by the immediate addition of 0.08 ml (1.3 mmol) of methyl iodide in 3 ml of DME. The reaction mixture was worked up as usual and chromatographed on silica gel. Elution with pentane followed by more polar mixtures with benzene gave after naphthalene 330 mg of 3β-methoxycholest-5-ene. It had mp 78 °C (lit.[36] mp 84 °C); NMR (CCl_4) δ 0.71 (3 H, s, C-18 methyl), 1.06 (3 H, s, C-19 methyl), 3.20 (1 H, m, C-3 H), 3.26 (3 H, s, –OCH_3), 5.26 (1 H, m, C-6 H).

The methylation was carried out both in THF and in DME. The proportion of the methyl ether formed varied with solvent as well as the concentration of the reagent.

Similar methylations using naphthalene lithium and naphthalene potassium were also carried out. The results are given in Table II.

Acknowledgment. We wish to thank Ciba-Geigy Research Centre and Hindustan Lever Research Centre for NMR spectra and the former for microanalysis. We are grateful to Dr. W. W. Conover of Stanford University for the 360-MHz NMR spectrum.

Appendix

Additional evidence which strongly supports the mechanism given in Schemes V and VI has now been obtained. Reverse dropwise addition of **1c** in THF to naphthalene sodium in THF gave a 70 (±3):30(±3) ratio of **18a:18b**. This means that initial addition across the acetylene is syn and the corresponding vinyl radical is trapped by reduction to vinyl carbanion before it equilibrates to the extent that it does in normal addition. This is to be expected because of the excess of reducing agent present during the reverse addition. This dependency of ratio **18a:18b** on mode of addition would not be expected if there was equilibration at the vinyl carbanion stage. This possibility had been considered unlikely because of the results of vinyl halide reductions with naphthalene sodium.[32]

It also became essential to put the configurational assignment of **18a** and **18b** on a stronger footing. This has been done using 360-MHz NMR.[33] Decoupling with the vinyl hydrogen showed that the methyl of the ethylidene group of the major isomer occurs at δ 1.60 and has a distinctly smaller band-width at half height than the methyl at δ 1.75 due to the minor isomer. In the structure **18b** assigned to the latter, the methylene at C-2 is trans to the methyl and hence greater homoallylic coupling[34] is to be expected.

Registry No.—**1a,** 21489-86-1; **1b,** 17541-44-5; **1c,** 58502-98-0; **2c,** 58502-99-1; **5a,** 58503-00-7; **5c,** 52091-54-0; **5d,** 58503-01-8; **5e,** 58503-02-9; **6,** 52091-60-8; **7a,** 58503-03-0; **11,** 58503-04-1; **11** acetate, 58512-16-6; **12,** 58503-05-2; **13,** 58503-06-3; **14,** 58503-07-4; **15,** 58503-08-5; **16,** 58503-09-6; **17,** 58503-10-9; **18a,** 58503-11-0; **18b,** 58503-12-1; **19,** 24298-82-6; **20,** 58503-13-2; **21,** 58503-14-3; **22,** 58503-15-4; **23,** 58503-16-5; **23** 5α analogue, 58526-09-3; **24,** 58503-17-6; **25,** 58503-18-7; **26,** 58503-19-8; **27,** 58503-20-1; **28,** 58503-21-2; **29,** 58503-22-3; **30,** 58503-23-4; naphthalene sodium, 3481-12-7; naphthalene potassium, 4216-48-2; naphthalene lithium, 7308-67-0; 4,5-epoxy-4-methylcholestan-3-one, 58526-10-6; tosylhydrazine, 539-44-6; cholesterol, 57-88-7; methyl iodide, 74-88-4; 3β-methoxycholest-5-ene, 1174-92-1.

References and Notes

(1) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Am. Chem. Soc.*, **87,** 1148–1149 (1965).
(2) S. K. Pradhan, and V. M. Girijavallabhan, *Steroids,* **13,** 11–20 (1969).
(3) N. Y. Zachariah, unpublished work from Regional Research Laboratory, Hyderabad.
(4) (a) Presented in part at Symposium on "Reaction Mechanisms in Organic Chemistry" at the 62nd session of the Indian Science Congress, New Delhi, 1975; (b) partly abstracted from Ph.D. Dissertation of R. Subramanian, CSIR Fellow, University of Bombay, 1974.
(5) N. D. Scott, J. F. Walker, and V. L. Hansley, *J. Am. Chem. Soc.*, **58,** 2442–2444 (1936).
(6) For recent references, see L. L. Miller, *J. Chem. Educ.*, **48,** 168–173 (1971); N. L. Holy and J. D. Marcum, *Angew. Chem., Int. Ed. Engl.*, **10,** 115–124 (1971).
(7) (a) The mass spectrum of this gave no molecular ion peak. The highest peak at *m/e* 360 was formed by loss of 52 due to an extremely facile McLafferty rearrangement. An equally facile loss of 52 mass units was found with **1a.** (b) Disubstitution at C-6 was confirmed by NMR of **11** obtained by $NaBH_4$ reduction of **5a.**
(8) The O-methylation was examined further. See Table II.
(9) Only the overreduction product of **12** was obtained using Na–NH_3–*t*-BuOH.
(10) Spectral evidence is given in the Experimental Section. All partial formulas given henceforth refer to cholestane derivatives.
(11) D. Curotti and A. Romeo, *Gazz. Chim. Ital.*, **95,** 992–996 (1965).
(12) B. V. Cheney, *J. Am. Chem. Soc.*, **90,** 5386–5390 (1968). For a recent example, see S. K. Pradhan and V. M. Girijavallabhan, *Chem. Commun.*, 644–645 (1970).
(13) Reductive cyclization is not restricted to exo olefin formation. This is demonstrated by successful cyclization of cyclodecyn-6-one with Li–NH_3: R. J. Balf, B. Rao, and L. Weiler, *Can. J. Chem.*, **49,** 3135–3142 (1971).
(14) Sodamide formation has not been independently proved. Sodium hydride formations on bubbling hydrogen has been established. S. Bank and T. A. Lois, *J. Am. Chem. Soc.*, **90,** 4505–4506 (1968).
(15) We thank V. B. Thaker for a sample of **28.** The 5β configuration of this is based on its method of preparation and on its specific rotation. It has $[\alpha]D$ +102°, which compared with cholest-3-en-5β-ol, $[\alpha]D$ +94°, whereas cholest-3-en-5α-ol has $[\alpha]D$ –14° [A. Nickon and W. L. Mendelson, *Can. J. Chem.*, **43,** 1419–1428 (1965)].
(16) The radicals are assumed to be nonlinear with a relatively low energy barrier to inversion. (a) See review by L. A. Singer, *Sel. Org. Transform.*, **2,** 239–268 (1972); (b) G. D. Sargent and M. W. Browne, *J. Am. Chem. Soc.*, **89,** 2788–2790 (1967).
(17) H. O. House and E. F. Kinloch, *J. Org. Chem.*, **39,** 747–755 (1974), and references cited therein.
(18) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596–4604 (1957).
(19) W. M. Moore and D. G. Peters, *J. Am. Chem. Soc.*, **97,** 139–144 (1975).
(20) P. T. Lansbury, T. R. Demmin, G. E. DuBois, and V. R. Haddon, *J. Am. Chem. Soc.*, **97,** 394–403 (1975). See note 15 on p 402.
(21) Review by S. I. Miller and R. Tanaka, *Sel. Org. Transform.*, **1,** 143–238 (1970).
(22) $E_{1/2}$ for substituted acetylenes is estimated to be more negative than –3.0 V (vs. SCE) by House (ref 17) while that for acetone is –2.1 V according to C. L. Perrin, *Prog. Phys. Org. Chem.*, **3,** 165–316 (1965).
(23) D. A. Dadley and A. G. Evans, *J. Chem. Soc. B,* 418–422 (1967); D. A.

Dadley and A. G. Evans, *ibid.*, 107–111 (1968); A. Rainis and M. Szwarc, *J. Am. Chem. Soc.*, **96**, 3008–3010 (1974).
(24) There appear to be no reports of reactions with α,β-unsaturated ketones either. Preliminary work in our laboratory indicates formation of roughly equal amounts of saturated ketone and pinacol.
(25) C. D. Gutsche, I. Y. C. Tao, and J. Kozma, *J. Org. Chem.*, **32**, 1782–1790 (1967).
(26) It is worth noting that no intramolecular nucleophilic attack by the alkoxide on the acetylene takes place under the reaction conditions.
(27) S. Bank and B. Bockrath, *J. Am. Chem. Soc.*, **93**, 430–437 (1971).
(28) J. K. Crandall and D. J. Keyton, *Tetrahedron Lett.*, 1653–1656 (1969), report cyclization of 5-undecynyl radical to hexylidene cyclopentane. The 6-dodecynyl radical failed to cyclize. Successful cyclization to **26** must reflect primarily the greater stability of the radical ion, though greater rigidity in the steroid molecule may also contribute.
(29) It is not implied that endo double bond formation is prohibited. Hence there is no contradiction with results reported in ref 13.
(30) A proton abstracted from the solvent by the radical ion is expected to be removed from circulation very rapidly by the vinyl carbanion or the reagent.
(31) K. Suga, S. Watanabe, and T. Suzuki, *Can. J. Chem.*, **46**, 3041–3045 (1968); S. Watanabe, K. Suga, T. Fujita, and K. Fujiyoshi, *Chem. Ind. (London)*, 1811 (1969).
(32) Observations by G. D. Sargent and M. W. Browne, *J. Am. Chem. Soc.*, **89**, 2788 (1967), taken in conjunction with those of A. J. Fry and M. Mitnick, *J. Am. Chem. Soc.*, **91**, 6207 (1969).
(33) The NMR was done in a Bruker HX-360 instrument at Stanford University. We are grateful to Dr. H. J. Ringold for arranging the determination.
(34) R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960).
(35) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402–3403 (1962).
(36) I. M. Klotz, *J. Am. Chem. Soc.*, **66**, 88–89 (1944).

Nucleophilic Additions to Aldehydes and Ketones. 2.[1] Reactions of Heterocyclic Aldehydes with Hydroxide Ions

W. J. Scott, W. J. Bover,[3] K. Bratin,[4] and P. Zuman*[2]

Department of Chemistry, Clarkson College of Technology, Potsdam, New York 13676

Received July 30, 1975

Three groups of heterocyclic carboxaldehydes can be distinguished according to their reactivity toward hydroxide ions: to the first group belong nonhydrated five-membered heterocyclic aldehydes (derivatives of furan, thiophene, and N-substituted pyrrole) which add hydroxide ions to the carbon–oxygen double bond in a similar way as benzaldehydes. The second groups consists of pyrrole and indole derivatives where in alkaline media the NH group dissociates before the formyl group is attacked. Hydrated aldehydes (pyridine, thiazole, and imidazole derivatives) belonging to the third group show dissociation of the geminal diol. Equilibrium constants of these three types of reactions were measured spectrophotometrically. Most of the aldehydes studied undergo electrooxidation as geminal diol anions which was followed polarographically. Ring substituents and the nature of the heteroatom affect the values of equilibrium constants and half-wave potentials. In indole and pyrrole derivatives a specific interaction between the formyl group and the heterocycle is indicated.

In previous work[5] an acidity scale J_- has been developed to be used in strongly alkaline media for reactions involving addition of hydroxide ions. Some meta- and para-substituted benzaldehydes have been used as indicators for characterizing acidity of aqueous sodium hydroxide solutions. By means of this scale thermodynamic equilibrium constants for hydroxide ion additions to other meta- and para-substituted benzaldehydes were determined.[1] Corresponding pK values were correlated with Hammett substituent constants σ by means of a reaction constant $\rho = 2.76$ [$r = 0.994$, S (est) 0.012]. Later Greenzaid[6] also measured spectrophotometrically the ratio of concentrations of the anion of the geminal diol to that of the free aldehydic form. The concentration of an unspecified hydroxide was used in calculation of equilibrium constants of the reaction 1

$$\mathrm{ArCHO} + \mathrm{OH^-} \overset{K}{\rightleftharpoons} \mathrm{ArCH(OH)O^-} \qquad (1)$$

instead of acidity functions and the activity term $y_{\mathrm{ArCH(O^-)OH}}/y_{\mathrm{ArCHO}}y_{\mathrm{OH^-}}$ was neglected. This approach restricted the study to solutions of the unspecified base below 1.5 M and this in turn limited the investigation to compounds with electronegative substituents. Reported values could have been considered as practical equilibrium constants, provided that ionic strength was kept constant. As this was not the case, the values reported by Greenzaid[6] correspond for each compound to another ionic strength and hence can be considered only as "crude practical constants". Correlation of these approximate values for the limited group of monosubstituted and some disubstituted benzaldehydes accessible to measurement with Hammett substituent constants σ greater than zero, gave $\rho = 2.24$ ($r = 0.982$). The susceptibility of benzaldehydes to substituent effects for hydroxide addition is similar to that for methoxide addition, reported recently.[7]

The anion of the geminal diol has been proved[8] to be the electroactive form in the electrooxidation of benzaldehydes in alkaline media. Rate constants for the addition of the hydroxide ion and the reverse reaction obtained from polarographic data on benzaldehyde oxidations were about 1.5 orders of magnitude larger than values for 3- and 4-chlorobenzaldehydes measured by stopped-flow technique.[9] This difference might reflect different reaction conditions used, but also may be caused by the effect of the electric field in the vicinity of the electrode. Another electrochemical method, based on constant potential electrolysis of the corresponding aromatic acid at a rotating disc electrode at pH 6.2, was proposed.[10] The rate constants found[10] for 3-chlorobenzaldehyde which are seven to eight orders of magnitude smaller than those above were attributed to loss of water rather than OH^-. Since pH dependence of these constants has not been studied, it is not possible to comment on their attribution, but the value of the equilibrium constant, indicating that about 50% of 3-chlorobenzaldehyde exists in hydrated form, is clearly doubtful.

In this contribution both the studies of the equilibria involving addition of hydroxide and the electrooxidation of the aldehydic group are extended to heterocyclic compounds bearing an aldehydic group. Attention is being paid to the role of the nature of the heterocyclic ring and effect of substituents as well as to competitive reactions.

Experimental Section

Chemicals and Solutions. Fural, 5-methylfural, 5-hydroxymethylfural, 2-thiophenecarboxaldehyde, 3-methyl-2-thiophenecarboxaldehyde, 5-bromo-2-thiophenecarboxaldehyde, 2-pyrrolecarboxaldehyde, *N*-methyl-2-pyrrolecarboxaldehyde, 3-indolecarboxaldehyde, *N*-benzyl-3-indolecarboxaldehyde, *N*-ethyl-3-carbazolecarboxaldehyde, and 3-cinnolinecarboxaldehyde (Aldrich Chemical Co.), *N*-phenyl-2,5-dimethyl-3-pyrrolecarboxaldehyde