Homoallylic Free Radicals. A Study of the Rearrangement of 3,5-Cyclocholestanyl Radical to Cholesteryl Radical[1]

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Abstract: A study of the reaction of cholesteryl chloride (VI) and 3,5-cyclocholestan-6-yl chloride (VII) with triphenyltin hydride and with sodium biphenyl radical anion has been carried out. With each of these reducing agents, cholesteryl chloride yields only 5-cholestene (VIII). On the other hand, cyclocholestanyl chloride gives mixtures of 3,5-cyclocholestane (IX) and 5-cholestene with both reducing agents. The results have been interpreted in terms of the formation of intermediate classical radicals which have the option of rearrangement or capture. The addition of thiophenol to 6-methylenecyclocholestane (III) has been studied briefly. This gives a mixture of products which on treatment with Raney nickel leads to 6-methylcyclocholestane (IV) and 6-methyl-5-cholestene (V). The results demonstrate without question that cholesteryl radical is significantly more stable than cyclocholestanyl radical.

Homoallylic carbonium ion systems have received considerable attention in recent years,[2] although it is still clear that the intermediates involved have not yet been defined to the complete satisfaction of all of the workers in this field.

On the other hand, although there has been a great deal less activity in homoallylic free-radical systems and their interconversions with the corresponding cyclopropylcarbinyl systems, there appears to be more agreement regarding the classical nature of the free-radical intermediates. Brown and Borkowski[3] and Roberts and his coworkers[4] have studied the photochlorination of methylcyclopropane. Reaction in the liquid phase gave only cyclopropylcarbinyl chloride, while reaction in the vapor phase gave mixtures of cyclopropylcarbinyl chloride and allylcarbinyl chloride. Labeling experiments[4] were consistent with classical radical intermediates. Cristol, Brindell, and Reeder[5] showed that free-radical addition to norbornadiene gave mixtures of dehydronorbornyl and nortricyclyl derivatives and that the ratio of products was dependent upon the lifetime of the intermediate carbon radicals. Thus, they showed that a substituted dehydronorbornyl radical rearranged to a nortricyclyl radical if chain transfer did not intervene rapidly. Similar results were observed by Cristol and Reeder,[6] by Brace,[7] by Trecker and Henry,[8] and by Cristol and Davies.[9] Studies of a similar nature include radical additions to methylenenorbornene[10,11] and to 2-cyclopropylpropene[12] and decarbonylation of *endo*-dehydronorbornyl-5-carboxaldehyde.[13] Reduction of dehydronorbornyl and nortricyclyl halides with tin hydrides[14] showed that the rearrangement of the radicals was a reversible process. All of these results can be readily accommodated by assuming discrete classical radical intermediates, and it has not been found necessary to invoke any type of delocalized radical intermediates. Instead, these are clearly simply transition states between classical radicals.

More recently,[15,16] cyclopropylcarbinyl radicals have been proposed as intermediates in rearrangements from one homoallyl radical to another.

In view of the considerable interest in the carbonium ion interconversions of steroidal systems such as the 3-cholesteryl and 3,5-cyclocholestanyl species,[17] we thought it would be interesting to look at some reactions involving the analogous free-radical intermediates.

Our plans to generate the desired cholesteryl I and 3,5-cyclocholestanyl II radicals by decomposition of the

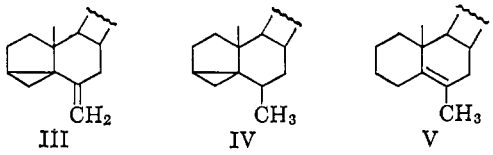
I II

corresponding acyl peroxides and carboxaldehydes were abandoned as the unknown 3,5-cyclocholestanyl compounds eluded our attempts at synthesis.

We then decided to look at the addition of thiophenol to 6-methylene-3,5-cyclocholestane (III). A mixture of thioethers resulted, which we were unable to separate by chromatography on either neutral alumina or silica gel. Oxidation of this thioether mixture to the corresponding sulfone mixture yielded a yellow oil from which no pure compounds could be isolated. Desulfurization of the thioether mixture with W-2 Raney nickel in aqueous dioxane and subsequent chromatog-

(1) A preliminary communication of a portion of this work has already appeared: S. J. Cristol and R. V. Barbour, *J. Am. Chem. Soc.*, **88**, 4262 (1966).
(2) See R. Breslow in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 259 ff, and references therein.
(3) H. C. Brown and M. Borkowski, *J. Am. Chem. Soc.*, **74**, 1894 (1952).
(4) E. Renk, P. R. Shafer, W. H. Graham, R. H. Mazur, and J. D. Roberts, *ibid.*, **83**, 1987 (1961).
(5) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *ibid.*, **80**, 635 (1958).
(6) S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, **26**, 2182 (1961).
(7) N. O. Brace, *ibid.*, **27**, 3027 (1962).
(8) D. J. Trecker and J. P. Henry, *J. Am. Chem. Soc.*, **85**, 3204 (1963).
(9) S. J. Cristol and D. I. Davies, *J. Org. Chem.*, **29**, 1282 (1964).
(10) E. S. Huyser and G. Echegaray, *ibid.*, **27**, 429 (1962).
(11) S. J. Cristol, T. W. Russell, and D. I. Davies, *ibid.*, **30**, 207 (1965).
(12) E. S. Huyser and J. D. Taliaferro, *ibid.*, **28**, 3442 (1963).
(13) J. W. Wilt and A. A. Levin, *ibid.*, **27**, 2319 (1962).
(14) C. R. Warner, R. J. Strunk, and H. G. Kuivila, *ibid.*, **31**, 3381 (1966).
(15) L. H. Slaugh, *J. Am. Chem. Soc.*, **87**, 1522 (1965).
(16) (a) J. A. Claisse, D. I. Davies, and C. K. Alden, *J. Chem. Soc.*, 1498 (1966); (b) L. K. Montgomery, J. W. Matt, and M. R. Webster, *J. Am. Chem. Soc.*, **89**, 923 (1967).
(17) See N. L. Wendler in "Molecular Rearrangements," Part II, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 1075 ff.

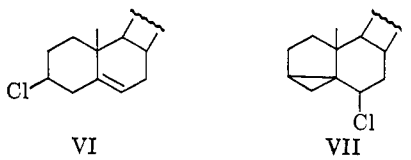
raphy on neutral alumina impregnated with 10% silver nitrate resulted in the isolation of a 12% yield of 6-methyl-3,5-cyclocholestane (IV) and a 21% yield of 6-methylcholest-5-ene (V). These materials were identified by comparison with pure samples prepared by alternate routes.



III IV V

These results made it clear that there was rearrangement from the original cyclocholestanyl radical to the cholesteryl radical, but in view of the facts that the hydrocarbons IV and V were isolated in poor yield and the thioethers were not separable, we decided not to carry on with this approach to the problem.

Reductions with Triphenyltin Hydride. A considerable body of evidence has been accumulated by Kuivila and his coworkers[18-20] establishing the free-radical chain course for the reduction of organic halides by organotin hydrides. Thus it appeared that the desired radicals I and II could be generated by reduction of 3β-chlorocholest-5-ene (cholesteryl chloride, VI) and 6β-chloro-3α,5α-cyclocholestane (cyclocholestanyl chloride, VII), respectively. These chlorides were readily prepared by the procedure of Kosower and Winstein[21] and these authors have also described procedures for determining the composition of mixtures of VI and VII.



VI VII

As reaction of alkyl halides with triphenyltin hydride leads to hydrocarbon products, it was necessary to have the hydrocarbons 5-cholestene (VIII)[22] and 3α,5α-cyclocholestane (IX)[23] to work out analytical procedures. We decided to make these hydrocarbons for the purposes of identification and analysis using the carbonium ion trapping procedure of Brown and Bell.[24] Thus, cholesteryl *p*-toluenesulfonate was solvolyzed in aqueous diglyme containing sodium borohydride and sodium hydroxide. The hydrocarbon product was a mixture containing 42% cyclocholestane (IX) and 15% 5-cholestene (VIII). Thus, as might be anticipated from reactions with other nucleophiles,[25-30] the carbonium ion intermediate(s) is captured to a greater extent at C-6 than at C-3 by borohydride. We found that the hydrocarbon mixture was readily separated on a column of 10% silver nitrate on alumina.[31] The cycloparaffin was eluted with *n*-pentane and the olefin could then be obtained by elution with 5% benzene in petroleum ether (bp 60–70°).


VIII IX

When we tried to reduce cyclocholestanyl chloride (VII) with triphenyltin hydride in refluxing benzene, the conditions first described for such reductions, we observed that the chloride rearranged to cholesteryl chloride (VI), presumably *via* an ion-pair process. Chloride VII was so unstable, in fact, that a benzene solution rearranged to a mixture of 62% VI and 38% VII in 24 hr at room temperature. The rearrangement was followed quantitatively by titration for chloride ion using the procedure of Kosower and Winstein[21] and was observed to follow first-order kinetics ($k \sim 1 \times 10^{-5}$ sec^{-1} at 26°). Kosower and Winstein have shown that there is much ion-pair return in the solvolysis of VII, even in 90% dioxane.

On the other hand, when the chloride VII was allowed to stand at room temperature in *n*-pentane, no rearrangement to VI occurred, even in the presence of large quantities of triphenyltin chloride. In addition, it was observed that the tin hydride reduction reaction proceeded quite well at room temperature or at lower temperatures in *n*-pentane, if the reaction was carried out under irradiation by a 60-W tungsten light bulb. The reductions proceeded quite smoothly and in good yield at room temperature, although incomplete reduction occurred at lower temperatures in the time we used (24 hr). The hydrocarbons were then analyzed as described above.

Table I gives the results of these reductions at various temperatures and at various tin hydride concentrations. Several important observations should be made about these results. It may be noted that radical rearrangement does indeed occur in this system, but that the rearrangement is a one-way process. Thus, reduction

Table I. Reduction of Cholesteryl Chloride (VI) and 3,5-Cyclocholestan-6-yl Chloride (VII) by Triphenyltin Hydride in *n*-Pentane

Expt	Chloride	Hydride concn, *M*	Temp, °C	IX, %	VIII, %	IX/VIII	Convrsn to hydrocarbon,[b] %
1	VI	0.08	15	0	100	0	8
2	VII[a]	0.04	15	1	99	0.01	65
3	VII[a]	0.40	15	4	96	0.04	75
4	VII[a]	Neat	30	13	87	0.16	68
5	VII[a]	0.08	−20	18	82	0.22	17
6	VII[a]	1.0	−15	30	70	0.43	14

[a] The material used was a mixture of approximately 80% VII and 20% VI, as shown by the analytical procedure of Kosower and Winstein.[21] [b] Based on starting chloride. Excess tin hydride was present in all cases.

(18) H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Am. Chem. Soc.*, **84**, 3584 (1962).
(19) H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963).
(20) L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.*, **86**, 3047 (1964).
(21) E. M. Kosower and S. Winstein, *ibid.*, **78**, 4354 (1956).
(22) W. G. Dauben and K. H. Takemura, *ibid.*, **75**, 6302 (1953).
(23) F. S. Prout and B. Riegel, *ibid.*, **74**, 3190 (1952).
(24) H. C. Brown and H. M. Bell, *J. Org. Chem.*, **27**, 1928 (1962).
(25) W. Stoll, *Z. Physiol. Chem.*, **207**, 147 (1932).
(26) I. M. Heilbron, J. Hodges, and F. S. Spring, *J. Chem. Soc.*, 759 (1938), and preceding papers.
(27) S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).
(28) S. Winstein and A. H. Schlesinger, *ibid.*, **70**, 3528 (1948).
(29) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).
(30) C. W. Shoppee, *Bull. Soc. Chim. France*, [5] **18**, C 122 (1951).
(31) L. R. Chapman and D. F. Kuemmel, *Anal. Chem.*, **37**, 1598 (1965).

Table II. Reduction of Cholesteryl Chloride (VI) and Cyclocholestanyl Chloride (VII) with Sodium Biphenyl

Expt	Chloride	Solvent	Radical anion[a] concn	Temp, °C	IX, %	VIII, %	Total yield of VIII and IX,[e] %
1	VI	Glyme	Low	25	0	100	75
2	VI	Glyme	High	25	0	100	71
3	VII[b]	Glyme	Low	25	11	89	72
4	VII[b]	Glyme	High	25	20	80	82
5	VII[b]	Benzene[c]	Low	25	10	90	58
6	VII[b]	Toluene[c]	Low	25	10	90	62
7	VII[b]	Tetralin[c]	Low	25	10	90	70
8	VII[b]	Ph_3SnH[d]	Low	25	11	89	58
9	VII[b]	Glyme	Low	−20	28	72	84
10	VII[b]	Glyme	Low	−70	31	69	77
11	VII[b]	Glyme	High	−20	41	59	84
12	VII[b]	Glyme	High	−70	60	40	70

[a] "Low" concentration refers to addition of sodium biphenyl to chloride solution; "high" concentration refers to the reverse mode of addition. [b] This was a mixture of approximately 80% VII and 20% VI. [c] These solutions contained 1 *M* glyme. [d] This solution was 1 *M* Ph_3SnH and approximately 1 *M* glyme in benzene. [e] Based on starting chloride.

starting with cholesteryl chloride (VI) gives only 5-cholestene (VIII). Cyclocholestanyl chloride (VII) gives largely VIII, but in addition affords some unrearranged hydrocarbon IX. Thus we have succeeded in trapping II before complete rearrangement to its homoallyl isomer I. As the transition state for the rearrangement of the radicals to each other is obviously the same in either direction, it is clear that these results are compatible only with a significantly greater stability of the cholesteryl radical I compared with the cyclocholestanyl radical II. It is of course equally clear that these reductions cannot involve a nonclassical radical intermediate, as such an intermediate would yield the same mixture from each halide.

A similar conclusion can be drawn from the effect of hydride concentration upon the composition of the hydrocarbon mixture. With lower concentrations of hydride the lifetime of the radical before chain transfer is increased and there is therefore more opportunity for rearrangement from II to I. This may be noted by comparing the results of experiments 2 and 3 and those of experiments 5 and 6, as well as that of experiment 4. With higher hydride concentrations more of radical II is captured than at low hydride concentrations and the ratio of IX to VIII increases. The temperature effect is interesting as it shows that the activation energy for radical rearrangement is greater than that for hydride transfer. By combining high hydride concentrations with low temperatures we succeeded in obtaining as much as 30% of unrearranged hydrocarbon IX.

Reduction with Sodium Biphenyl Radical Anion. The use of radical anions for the production of halide ion from alkyl halides as a part of the quantitative determination of halogen has been developed by several workers. Benton and Hamill[32] described the use of sodium naphthalene and later Liggett[33] developed the use of sodium biphenyl in glyme (1,2-dimethoxyethane) for the quantitative removal of halogen atoms. These workers did not concern themselves with the fate of the organic fragment of the alkyl halide.

Warhurst and his coworkers[34] studied the reactivities of various alkyl and aryl halides with a variety of radical anions. Their data led them to conclude that radicals were involved as reaction intermediates from the organic halides but very little was done to learn of the fate of the organic radicals. In our laboratory[35] we have used a solution of sodium biphenyl in glyme to remove chlorine from organic molecules. In the work referred to, we showed that the organic product was one in which the chlorine atom had been replaced by a hydrogen atom.

The evidence available to us suggested that it would be interesting to treat chlorides VI and VII with a solution of sodium biphenyl radical anion as a means of generating the radicals I and II. At the time we began the work, we considered it likely that the radical intermediate would be trapped by the solvent molecule by hydrogen atom transfer. As will be seen below, that is not the case but instead the radical is trapped by another molecule of radical anion. The purpose of the work was similar to that with the hydride reduction, namely, that of showing that both radicals I and II were independent species. Our work has already been published in preliminary form.[1]

The reduction reactions were carried out by two different procedures. In procedure 1, a solution of the chloride in glyme was added dropwise to a 1 *M* solution of the radical anion in a reaction flask maintained at the desired temperature and under an atmosphere of purified, dry nitrogen. The results using this procedure are marked in Table II as having a "high" concentration of biphenyl radical anion. In the second procedure, a solution of the radical anion was added dropwise to a solution of the chloride in glyme at a controlled temperature and under a nitrogen atmosphere. These runs are described as having a "low" concentration of radical anion. The intention of the two procedures was to determine whether the ratio of reduction products IX/VIII was sensitive to the concentration of radical anion present. Unfortunately, the reaction between alkyl halide and radical anion is very rapid so that the reaction in the "low" situation is over before the drop is completely dispersed in the reaction medium. This means that, although the concentration for the "low" system would be about 0.01 *M* in radical anion

(32) F. L. Benton and W. H. Hamill, *Anal. Chem.*, **20**, 269 (1948).
(33) L. M. Liggett, *ibid.*, **26**, 748 (1954).
(34) See, *inter alia:* (a) D. J. Morantz and E. Warhurst, *Trans. Faraday Soc.*, **51**, 1375 (1955); (b) H. V. Carter, B. J. McClelland, and E. Warhurst, *ibid.*, **56**, 343 (1960); (c) A. Mathias and E. Warhurst, *ibid.*, **56**, 348 (1960).
(35) See, for example, S. J. Cristol, F. P. Parungo, and D. E. Plorde, *J. Am. Chem. Soc.*, **87**, 2870 (1965).

if the drop were completely dispersed, it lies between that concentration and 1 *M* in actual fact.

A similar situation of course obtains in the "high" concentration situation, where at the interface between the solution of alkyl halide and that of the radical anion the concentration of radical anion is well below that for the gross solution. In spite of these difficulties, as may be seen in Table II, significant differences in product composition are observed under the "high" and "low" concentration conditions.

Analysis for products was carried out substantially as described for the triphenyltin hydride experiments, except that removal of the biphenyl by steam distillation preceded analysis of the hydrocarbon products by chromatography on silver nitrate impregnated alumina.

It should be noted, from experiments 4–8, that the composition of the hydrocarbon product mixture was substantially independent of the solvent. This varied from pure dimethoxyethane (glyme) to a 1 *M* solution of glyme in benzene, in toluene, and in tetralin, and to a solution 1 *M* in triphenyltin hydride and 1 *M* in glyme in benzene. We felt that this variety of solvents differed substantially in hydrogen atom donating ability.[36] This suggests to us that the radicals formed by reduction with the radical anion or by rearrangement of the original radical are not captured by hydrogen transfer from the solvent, but instead are captured by electron transfer from another molecule of radical anion. This idea seems confirmed by a comparison of results at "low" and "high" concentrations of radical anion (compare experiments 3 and 4, 9 and 11, and 10 and 12). In each of these pairs, as the radical anion concentration is decreased, the extent of rearrangement is increased. These results are obviously consistent only with the formation of one radical intermediate (II) which may rearrange to the other radical intermediate (I) or which may be reduced by electron capture from another molecule of radical anion to a carbanion which resists further rearrangement. Presumably, each carbanion accepts a proton from the solvent faster than it rearranges.

As with the triphenyltin hydride hydrogen atom transfer, there is substantially less rearrangement at the lower temperatures than at the higher temperatures. Thus, as before, the rearrangement reaction has a higher activation energy than the electron-transfer reaction.

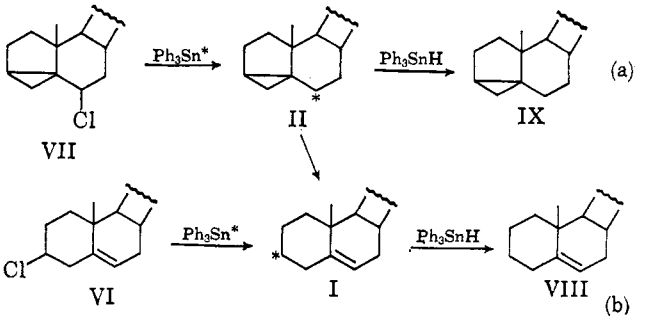
Discussion of Results

The results of the reduction experiments on halides VI and VII by both triphenyltin hydride and sodium biphenyl radical anion leads to the conclusion that, from VII, there is formed the classical radical II, which in a finite period of time may rearrange to the more stable classical radical I. This agrees with work reported on other homoallyllic and cyclopropylcarbinyl radical systems. In the present system, it is clear that the cholesteryl radical is more stable than the cyclocholestanyl radical, since all rearrangements observed proceed from II to I. No back rearrangement was observed. The differing results with VI and VII make it adequately clear that a nonclassical radical need not be considered as anything but a transition state between II and I.

The chain portion of the reduction of VI and VII by triphenyltin hydride may be pictured as shown in

(36) R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3754 (1963).

Scheme I

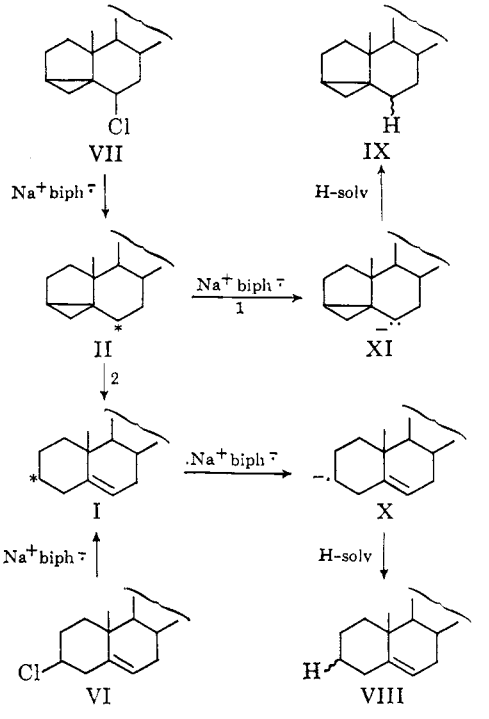


Scheme I. Consistent with this scheme is the observation that, in the reduction of VII, increasing concentrations of tin hydride lead to increased amounts of unrearranged hydrocarbon IX.

As mentioned above, the observation that a decreased temperature leads to decreased rearrangement is readily explainable by assuming that the activation energy for rearrangement is higher than that for chain transfer.

The reaction sequence which we have proposed[1] for the reduction of halides VI and VII by sodium biphenyl radical anion is outlined in Scheme II. It would appear

Scheme II



that the reaction begins by the transfer of an electron from the radical anion to the chlorine atom of the alkyl halide. Our data do not offer any evidence regarding the question of whether this electron transfer is accompanied by bond cleavage of the carbon–chlorine bond to give an alkyl radical and chloride ion or whether this step occurs subsequent to the initial electron transfer.[37] In any case, a free radical is formed.

If we consider the cyclocholestanyl case, the chloride VII forms the radical II. This radical would appear to have three important choices: (a) it may abstract a

(37) The data of Warhurst[34] on the rates of reaction of a number of alkyl halides with radical anions, in which there appears to be only very small reactivity differences due to structural variations, suggest that the carbon–chlorine bond is not broken in the electron-transfer step but that it occurs in a subsequent fast step.

hydrogen atom from the surrounding medium to give the cyclocholestane IX, (b) it may be reduced by another molecule of radical anion to form the corresponding carbanion XI, or (c) it may rearrange to the allylcarbinyl (cholesteryl) radical I which may have similar choices. That choice a is unimportant is shown by the lack of dependency of the product ratio on the hydrogen atom donor ability of the medium. Competition between the other choices is required to rationalize our results.

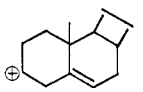
Thus, it would be predicted from this sequence that increased radical anion concentration should favor conversion of radical II to the carbanion XI over its isomerization to the radical I, as is observed. The dependence upon concentration also requires that the rearrangement occurs at the radical stage rather than at the carbanion stage. Thus, if all radical II were reduced to carbanion XI, a decrease in radical anion concentration should not lead to increased amounts of VIII.

Just as with the hydride reduction, the strong temperature dependence of the product ratio IX to VIII is a reflection of the difference in activation energies between the electron-transfer reaction and the rearrangement reaction.

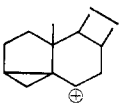
The interpretation which we have given to the work with sodium biphenyl radical anion is very similar to that which Garst and his coworkers[38] have given to their system. They studied the reaction of sodium naphthalene radical anion with 5-hexenyl and cyclopentylmethyl bromides and chlorides. In their case, the olefinic halide gave mixtures of 1-hexene and methylcyclopentane in the C-6 hydrocarbon products while only the latter C-6 hydrocarbon was observed in the reaction of the halomethylcyclopentanes. This case differs from ours in detail, but is similar to ours in the fact that electron transfer from a radical anion results in the formation of a free radical and halide ion. The olefinic radical which results is partially cyclized to cyclopentylmethyl radical and the two organic radicals are converted by a second mole of radical anion to carbanions which are then protonated by solvent.

It is of some interest to compare the results of radical reactions with those involving carbonium ion intermediates in the cyclocholestanyl–cholesteryl system. The latter have been discussed in detail by Winstein and Kosower.[39] The carbonium ion system[40] is a very labile one, and one which can lead, *via* kinetic control, to cyclocholestanyl derivatives from either cyclocholestanyl or cholesteryl reagents and *via* thermodynamic control to cholesteryl products. Put another way, the carbonium ion intermediate(s) formed from either starting system partition(s) itself (themselves) to give largely cyclocholestanyl products, suggesting that (if a nonclassical intermediate is assumed) a large fraction of the cationic charge is at C-6. If the classical formulation is assumed, the interpretation would be modified by stating that the cyclocholestanyl cation XIII appears to be thermodynamically more stable than the cholesteryl cation XII.[42]

On the other hand, our work shows that the free radicals have thermodynamic stabilities in the opposite sense (like the covalent compounds[39] VI and VII) in



XII



XIII

that the cholesteryl radical I is more stable than its isomer II.

Experimental Section

Reagents and Instruments. All melting points were corrected. Pmr spectra were determined on a Varian Model A-60 instrument at 60 Mc; chemical shift data are given in τ units relative to tetramethylsilane (τ = 10.00); coupling constants are observed. Optical rotations were determined on a Rudolph Model 70 polarimeter. *n*-Pentane was purified by vigorous stirring with batches of concentrated sulfuric acid until the acid layer remained colorless and was then distilled, bp 30–32° (630 mm). Triphenyltin hydride was prepared as described by Kuivila and Beumel.[43] Alumina was impregnated with 10% silver nitrate for chromatography substantially as described by Chapman and Kuemmel.[31]

Cholesteryl chloride (VI) was prepared substantially as described by Heilbron.[44] It had mp 95–96°, $[\alpha]^{26}D$ −32° ($CHCl_3$) (lit.[21] mp 95.5–96.5°, $[\alpha]^{23}D$ −31°). 3,5-Cyclocholestan-6-yl chloride (VII), mp 77–80°, $[\alpha]^{25}D$ +25° (CCl_4), was prepared as described by Kosower and Winstein,[21] who reported mp 73–78°, $[\alpha]^{24}D$ +29°. Kosower and Winstein reported that their product contained about 84% VII and 16% VI, using titrations for "active chloride." By their analytical procedure, our preparation analyzed for 80 ± 3% VII and 17 ± 3% VI.

Reductive Solvolysis of Cyclocholestanyl Chloride (VII). Preparation of 5-Cholestene (VIII) and 3α,5α-Cyclocholestane (IX). Two hundred and fifty milliliters of purified diethylene glycol dimethyl ether (diglyme, distilled under reduced pressure from lithium aluminum hydride) was cooled to 5° in an ice bath. To the cold diglyme was slowly added 11.4 g (0.30 mol) of sodium borohydride, a solution of 2 g (0.05 mol) of sodium hydroxide in 50 ml of water, and 5.4 g (0.01 mol) of cholesteryl *p*-toluenesulfonate.[45] The flask was placed in an oil bath and heated, with constant stirring, at 50 ± 5° for 24 hr. The reaction mixture was poured into a 1-l. separatory funnel containing 500 ml of cold water and 50 ml of acetone. A vigorous reaction ensued, consuming the excess borohydride. The mixture in the separatory funnel was allowed to cool and was extracted three times with 100-ml portions of Skellysolve B (petroleum ether, bp 60–70°). The combined organic extracts were washed with three 100-ml portions of cold water and then dried over anhydrous magnesium sulfate. The dried solution was poured onto a column of 100 g of Merck neutral alumina, made up in Skellysolve B. It was eluted with 1 l. of Skellysolve B. Evaporation of the solvent left a clear oil. This was dissolved in purified *n*-pentane and placed on a 200-g column, made up in *n*-pentane, of 10% silver nitrate on alumina. The column was cooled by a water jacket. The column was eluted with 1 l. of purified *n*-pentane and 1 l. of 5% benzene in Skellysolve B.

From the pentane fractions was obtained 1.4 g (42%) of 3α,5α-cyclocholestane (IX). Recrystallization from acetone gave mp 78–79°, $[\alpha]^{25}D$ +76° ($CHCl_3$) (lit.[23] mp 78–79°, $[\alpha]^{22}D$ +78° ($CHCl_3$)).

The benzene–Skellysolve B fractions gave 0.5 g (15%) of 5-cholestene (VIII). Recrystallization from acetone gave VIII, mp 92–93°, $[\alpha]^{25}D$ −55° ($CHCl_3$) (lit.[22] mp 92–93°, $[\alpha]^{25}D$ −56° ($CHCl_3$)).

(38) J. F. Garst, P. W. Ayers, and R. C. Lamb, *J. Am. Chem. Soc.*, **88**, 4260 (1966).

(39) S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(40) The question of whether there is a nonclassical ion intermediate, whether this is simulated by a set of rapidly equilibrating classical ions, or whether there is only one classical cation which may undergo normal and geitonodesmic[41] reactions is not critical to our discussion and will be ignored.

(41) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Am. Chem. Soc.*, **87**, 2879 (1965).

(42) A similar statement appears possible if one considers XII and XIII as the principal resonance contributing structures to a nonclassical cation.[39]

(43) H. G. Kuivila and O. F. Beumel, *J. Am. Chem. Soc.*, **83**, 1246 (1961).

(44) I. M. Heilbron, K. M. Samant, and J. C. E. Simpson, *J. Chem. Soc.*, 1410 (1933).

(45) E. S. Wallis, E. Fernholz, and F. T. Gebhart, *J. Am. Chem. Soc.*, **59**, 137 (1937).

Reaction of Cholesteryl Chloride (VI) with Triphenyltin Hydride. Preparation of 5-Cholestene (VIII). Into a 250-ml, three-necked round-bottomed flask, equipped with a magnetic stirring bar, reflux condenser, and nitrogen inlet tube, was placed 125 ml of reagent grade benzene, 4 g (0.01 mol) of cholesteryl chloride, 7 g (0.02 mol) of triphenyltin hydride, and 0.5 g of azobisisobutyronitrile. The reaction mixture was heated at reflux for 16 hr, with constant sitrring and slow nitrogen sweep. Carbon tetrachloride (5 ml) was added, and the mixture was heated at reflux for another hour to consume any excess tin hydride. The residue, following evaporation, was placed under vacuum for 2 hr to remove the last traces of solvent. The residual yellow oil was dissolved in Skellysolve B (some insoluble material remained) and placed on a 200-g column of Merck neutral alumina. Elution with 1 l. of Skellysolve B yielded 3.4 g (93%) of 5-cholestene (VIII). Recrystallization from acetone gave mp 92–93°, $[\alpha]^{25}D$ −55° ($CHCl_3$).

Typical Procedure for Reaction of Chlorides VI and VII with Triphenyltin Hydride. A 100-ml quartz flask was equipped with a nitrogen inlet and outlet tube and a magnetic stirring bar. Into the flask was placed the amount of purified *n*-pentane and triphenyltin hydride, to give the desired concentration, and 810 mg (2 mmol) of the desired halide. The flask was immersed in a bath maintained at the desired temperature, the nitrogen sweep was begun, the stirrer was started, and irradiation by a 60-W clear tungsten bulb was commenced. This was allowed to react for 24 hr, whereupon the reaction mixture was poured directly onto a 100-g column of Merck neutral alumina and eluted rapidly with 1 l. of Skellysolve B. Occasionally, excess tin hydride decomposed on the column liberating small amounts of gas, presumably hydrogen. This did not, however, affect the chromatographic separation of the tin residues from the steroid halides and hydrocarbons. The Skellysolve B eluent was evaporated to dryness, dissolved in purified *n*-pentane, and placed on a 200-g column, packed in purified *n*-pentane, of 10% silver nitrate on alumina. The column was cooled by a water jacket. Elution with purified *n*-pentane into tared flasks, rotary evaporation of the solvent, and weighing gave a quantitative measure of the 3α,5α-cyclocholestane (IX), produced during the reduction. Elution with 5% benzene in Skellysolve B into tared flasks, rotary evaporation of the solvent, and weighing gave a quantitative measure of the 5-cholestene (VIII) produced. Data on the reductions are given in Table I.

Reaction of Cholesteryl Chloride (VI) and Cyclocholestanyl Chloride (VII) with Sodium Biphenyl. Procedure 1. Into a 100-ml, two-necked, round-bottomed flask, equipped with a nitrogen-inlet tube, dropping funnel, and magnetic stirring bar, was placed 20 ml of a 1 *M* solution of sodium biphenyl[33] in glyme. A solution, in 5 ml of the appropriate solvent, of 810 mg (2 mmol) of either chloride VI or VII was placed in the dropping funnel. The reaction flask was cooled to the desired temperature, stirring was begun, and a slow nitrogen sweep was commenced. The halide solution was added slowly, dropwise, over a period of several minutes, the dropping funnel was washed with a small amount of solvent, and the washings were drained into the reaction flask. No color change occurred during the reaction as excess radical anion was always present. The reaction mixture was stirred an additional 3 min and was then poured into a separatory funnel containing 100 ml of cold water. The organic material was extracted with three 100-ml portions of Skellysolve B. The combined extracts were placed in a 1-l., round-bottomed flask, and the solvent was removed by rotary evaporation. Water (600 ml) was added, and the biphenyl was removed by steam distillation, adding additional water as required. The residue in the steam distillation flask was dissolved in Skellysolve B, dried over anhydrous magnesium sulfate, and filtered and the solvent removed by evaporation. The oily residue (a mixture of VIII and IX) was dissolved in purified *n*-pentane and analyzed by chromatography as described for the hydride reductions. Results are given in Table II (these are described as "high" concentrations of radical anion).

Procedure 2. Into a 100-ml, two-necked, round-bottomed flask, equipped with a nitrogen-inlet tube, dropping funnel, and magnetic stirring bar, was placed 810 mg (2 mmol) of either chloride VI or VII and 20 ml of the desired solvent. A 1 *M* solution of sodium biphenyl in glyme (10 ml) was placed in the dropping funnel. The flask was placed in a bath at the desired temperature, and the nitrogen sweep and stirring were begun. The sodium biphenyl solution was added very slowly, dropwise, with rapid and vigorous sitrring. (The reaction was practically instantaneous, and the thorough mixing of each drop of radical anion solution with the alkyl halide solution was probably incomplete.) Table II refers to the radical anion concentration of these reactions as "low." After the addition was complete, the reaction mixture was stirred another 3 min and was then worked up as described in procedure 1.

Preparation of 6-Methylene-3α,5α-cyclocholestane (III). A 500-ml, three-necked, round-bottomed flask was equipped with a nitrogen-inlet tube, reflux condenser topped with a calcium chloride drying tube, a dropping funnel, and a magnetic stirring bar. Into the flask was placed 200 ml of anhydrous diethyl ether and 36 g (0.10 mol) of triphenylmethylphosphonium bromide.[46] The nitrogen sweep was started and the stirring begun. The flask was cooled to 0° in an ice bath, and 75 ml of a 1.2 *M* solution (0.09 mol) of *n*-butyllithium was rapidly pipetted in. The reaction mixture immediately turned a bright, canary yellow color. This yellow solution was stirred for 15 min at 0° and was then removed from the ice bath. A solution of 3.8 g (0.01 mol) of 3α,5α-cyclocholestan-6-one[29] in 75 ml of anhydrous diethyl ether was added dropwise over a period of 30 min. The dropping funnel was washed with 10 ml of ether, and the washings were drained into the reaction. The reaction mixture was stirred an additional 2 hr, whereupon 1.1 g (0.01 mol) of dry potassium *t*-butoxide was added.[47] The milky, yellow-white reaction mixture was then allowed to stir at room temperature, under continuous slow nitrogen sweep, for 18 hr.

The reflux condenser was replaced with a distilling head, and the ether was rapidly distilled out of the flask while being continuously replaced with dry tetrahydrofuran (distilled from lithium aluminum hydride) until the distillation temperature reached the boiling point of tetrahydrofuran, 61° (630 mm). This mixture was then heated at reflux for an additional 3 hr, poured into 400 ml of ice water in a 1-l. separatory funnel, and extracted three times with 100-ml portions of diethyl ether. The combined ethereal extracts were washed twice with 100-ml portions of cold water and once with 100 ml of a saturated sodium chloride solution, then dried over anhydrous magnesium sulfate. The ethereal solution was filtered to remove the drying agent, and the solvent was removed by distillation at reduced pressure. The remaining oil was dissolved in a minimum of *n*-pentane and was chromatographed on a water-cooled column of 150 g of Merck neutral alumina made up in *n*-pentane.

Elution with 500 ml of *n*-pentane gave a clear oil which, upon crystallization from acetone, gave 3.1 g (83%) of 6-methylene-3α,5α-cyclocholestane (III), mp 65–66°, $[\alpha]^{25}D$ +97° ($CHCl_3$) (lit.[48] mp 58–61°).

The pmr spectrum indicated a poorly resolved doublet for the methylene protons centered at τ 5.42 and an unresolved multiplet for the cyclopropane hydrogens centered at τ 9.65. The infrared spectrum showed a strong, sharp absorption at 1645 cm^{-1} corresponding to the methylene double bond.

Anal. Calcd for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 87.83; H, 12.24.

Preparation of 6α-Methyl-3α,5α-cyclocholestane (IV). A solution of 250 mg (0.65 mmol) of 6-methylene-3α,5α-cyclocholestane (III) in 100 ml of absolute ethyl alcohol was added to a prereduced suspension of platinum prepared in 50 ml of absolute ethanol from 100 mg of platinum oxide. Hydrogenation was carried out at atmospheric pressure, with shaking, for 3 hr. The uptake of hydrogen was very slow, and stopped completely at the end of the first hour.

The reaction mixture was filtered through Celite to remove the catalyst and the solvent removed by rotary evaporation. The residual oil crystallized upon standing. The solid was recrystallized from absolute ethanol to give 150 mg (60%) of 6α-methyl-3α,5α-cyclocholestane (IV), mp 84–85°, $[\alpha]^{25}D$ +34° ($CHCl_3$).

The pmr spectrum showed an unresolved multiplet centered at τ 9.65 for the cyclopropane hydrogens; the 6α-methyl protons were, however, indistinguishable. The infrared spectrum was extremely simple showing only the typical carbon–hydrogen absorptions at 2850–2950, 1470, 1380, and 1010 cm^{-1}.

Anal. Calcd for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.63; H, 12.47.

The configuration of the methyl group at C-6 was assigned by analogy with reactions of 3α,5α-cyclocholestan-6-one which appears to react preferentially on the β side of the steroid molecule.[49]

Preparation of 3β-Bromo-6-methyl-5-cholestene. In a three-necked flask was placed 50 ml of boiled (degassed) carbon tetra-

(46) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).

(47) *Cf.* M. Schlosser and K. F. Christman, *Angew. Chem.*, **76**, 683 (1964).

(48) Unpublished work of W. G. Dauben and G. H. Berezin, referred to in R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962).

(49) See examples cited by L. M. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., Inc., New York, N. Y., 1959, p 316.

chloride and 500 mg (1.3 mmol) of 6-methylene-3α,5α-cyclocholestane. The flask was then evacuated and filled with dry hydrogen bromide gas (the free volume in the system (45 ml) was calculated to contain 1.5 mmol of hydrobromic acid). The flask was left in darkness and stirring was begun. The hydrobromic acid was very rapidly taken up by the carbon tetrachloride solution, evidenced by the rapid drop in pressure in the flask (as indicated on a mercury manometer). The pressure in the reaction flask was maintained at atmospheric (630 mm) by the introduction of small amounts of nitrogen.

The reaction was allowed to stir vigorously overnight (10 hr) in the dark. The reaction mixture was poured into a 500-ml flask and the carbon tetrachloride removed by rotary evaporation at room temperature. A white solid resulted which was recrystallized from acetone to give a crop of white, plate-like crystals. The crystals were removed by suction filtration and dried under vacuum. The yield of 3β-bromo-6-methyl-5-cholestene was 447 mg (75%), mp 106–107°, $[\alpha]^{25}D$ −22° ($CHCl_3$).

This material was observed to give a strong, positive Beilstein test for halogen and to react instantly with alcoholic silver nitrate to give a heavy yellow-white precipitate. The material instantly decolorized a dilute solution of bromine in carbon tetrachloride, as is characteristic of the 5-ene steroids. The infrared spectrum of the compound confirmed the presence of the Δ^5 double bond, showing a weak absorption at 1670 cm^{-1}.

Anal. Calcd for $C_{28}H_{47}Br$: C, 72.54; H, 10.22; Br, 17.24. Found: C, 72.37; H, 10.20; Br, 17.15.

While 6-bromo-6-methyl-3α,5α-cyclocholestane could very possibly have been the initial product of this reaction, the 6-bromo compound would be expected to rearrange to the thermodynamically more stable product, 3β-bromo-6-methyl-5-cholestene. The configuration of the bromine atom at C-3 was assumed to be β since all previously reported examples of nucleophilic attack in the 3 position of *i*-steroid cations[17] involves stereospecific entry of the nucleophile in the β position.

Preparation of 6-Methyl-5-cholestene (V). Into a 250-ml, two-necked round-bottomed flask, equipped with a reflux condenser and a gas inlet tube, was placed 500 mg (1.4 mmol) of triphenyltin hydride, 200 mg (0.4 mmol) of 3β-bromo-6-methyl-5-cholestene, 500 mg (3.0 mmol) of azobisisobutyronitrile, and 100 ml of reagent grade benzene. The nitrogen sweep was begun, and the reaction mixture was heated at reflux for 15 hr.

The benzene solution was poured into a 500-ml, round-bottomed flask and the solvent removed by rotary evaporation. The white, crystalline residue was dissolved in *n*-pentane and chromatographed on a water-cooled, 150-g column of Merck neutral alumina made up in *n*-pentane. Elution with 750 ml of *n*-pentane yielded an oil which crystallized upon standing. Recrystallization of this solid from dry acetone yielded 97 mg (58%) of platelets of 6-methyl-5-cholestene (V), mp 101–102°, $[\alpha]^{25}D$ −64° ($CHCl_3$).

This material was observed to decolorize a dilute solution of bromine in carbon tetrachloride instantly, contrary to the behavior of 6α-methyl-3α,5α-cyclocholestane (IV).

Anal. Calcd for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.64; H, 12.40.

Addition of Thiophenol to 6-Methylene-3α,5α-cyclocholestane (III). Into a 250-ml, one-necked flask, equipped with a magnetic stirring bar and a reflux condenser, was placed 200 mg (0.5 mmol) of 6-methylene-3α,5α-cyclocholestane (III), 11 g (0.1 mol) of thiophenol, and 150 ml of reagent grade benzene. This solution was heated at reflux for 48 hr with constant stirring. The benzene was then removed by rotary evaporation and the thiophenol removed by gentle steam heating under high vacuum. To the residue in the flask was added 150 ml of distilled dioxane, 20 ml of distilled water, and a scoop of W-2 activity Raney nickel.[50] This slurry was heated at reflux for 48 hr with continuous stirring. The flask was cooled and the catalyst removed by suction filtration through a Celite pad (*Caution:* the catalyst is pyrophoric when dry). The filtrate was poured into 500 ml of cold water in a 1-l. separatory funnel and extracted three times with 100-ml portions of Skellysolve B, and the combined extracts were dried over anhydrous magnesium sulfate. The drying agent was removed by suction filtration and the solvent stripped off by rotary evaporation. The residue was dissolved in purified *n*-pentane and chromatographed on a water-cooled column of 150 g of 10% silver nitrate on alumina.

Elution with 1 l. of purified *n*-pentane yielded 24 mg (12%) of 6α-methyl-3α,5α-cyclocholestane (IV), identified by comparison with that described above. Elution with 1 l. of a solution of 5% benzene in Skellysolve B afforded 42 mg (21%) of 6-methyl-5-cholestene (V), identified by comparison with that described above.

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(50) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.