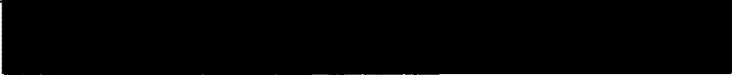AN ABSTRACT OF THE THESIS OF

<u>DALE DAVID DIXON</u>   for the   <u>DOCTOR OF PHILOSOPHY</u>
       (Name)   (Degree)

in <u>"CHEMISTRY (ORGANIC)"</u> presented on ⱵⱵⱵⱵⱵⱵ
        (Major)   (Date)

Title: <u>STEROID DIALKYLCARBENE REACTIONS</u>

Abstract approved: ███████████████████
                                Dr. F. T. Bond

Steroid carbenes have been investigated as synthetic inter-
mediates. Basic decomposition of 4-en-3-one tosylhydrazones (and
other A-ring systems) gives varying amounts of 2,4-dienes, and
solvent derived products with diglyme, heptane, tetrachloroethylene,
carbon tetrachloride, benzene and cyclohexene. A method for
separating complex product mixtures was developed and a study of
the effect of reaction conditions carried out. Butyl lithium decom-
position gives a high yield of the homoannular diene. Sterically
hindered carbenes give only intramolecular products.

Saturated steroid carbenes have been shown to give widely
varying γ/β insertion ratios. Decomposition of cholestan-3-one
tosylhydrazone in tetrachloroethylene results in the formation of a
solvent derieved pyrazoline. The possible role of pyrazolines in
other carbene reactions is discussed.

A facile route to interesting fused ring pyrazoles has been
developed in the 16-en-20-one tosylhydrazone system. With a

16-methyl system the pyrazolenine was isolated and investigated.

The possible biological properties of these compounds are discussed.

Steroid Dialkylcarbene Reactions

by

Dale David Dixon

A THESIS

submitted to

Oregon State University

in partial fulfillment of
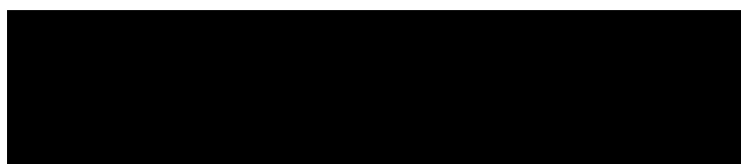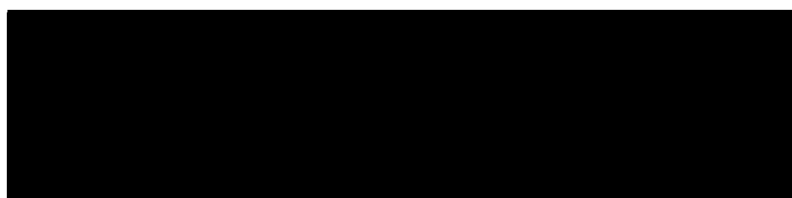the requirements for the
degree of

Doctor of Philosophy

June 1968

APPROVED:

███████████████

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Assistant Professor of Chemistry
                in charge of major

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Chairman of the Department of Chemistry

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Dean of Graduate School

Date thesis is presented _____ *May 14, 1965* _____

Typed by Gwendolyn Hansen for _____ Dale David Dixon _____

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF FIGURES

STEROID DIALKYLCARBENE REACTIONS

INTRODUCTION

The past decade has seen extensive study of carbenes as reaction intermediates. Carbenes are divalent, neutral species such as the parent system, methylene 1.

$$:C\begin{smallmatrix}H\\H\end{smallmatrix} \qquad :C\begin{smallmatrix}Cl\\Cl\end{smallmatrix} \qquad :C\begin{smallmatrix}R\\R\end{smallmatrix}$$

$$\underline{1} \qquad\qquad \underline{2} \qquad\qquad \underline{3}$$
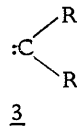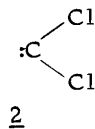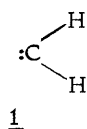
Although dichlorocarbene 2 was proposed as early as 1862 (57), extensive investigation of these intermediates has only been reported in the past fifteen years. Excellent summaries of early work are now available (72, 63) so that this introduction will focus primarily on points relevant to this thesis.

While many detailed studies have been made on the nature of the carbene species, this thesis is concerned primarily with the synthetic utility of dialkyl carbenes, 3. In the course of this work, numerous observations have been made concerning the reactivity of dialkyl carbenes, and these points will also be discussed.

Spin States of Carbenes

Two spin states are considered possible for the divalent, but electron deficient, carbene. Carbene intermediates may exist in a

singlet state with the two unshared electrons paired, or they may

exist as a triplet with the unshared electrons in separate orbitals.

Reactions of the triplet state should resemble radical reactions. The

singlet state, however, may show either electrophilic or nucleophilic

behavior depending on whether or not electron donating groups are

attached to the carbon atom. The triplet state with SP hybridization

is predicted and found to be linear, or nearly linear, while the singlet

carbene carbon adopts essentially SP^2 hybridization.

Triplet   Singlet
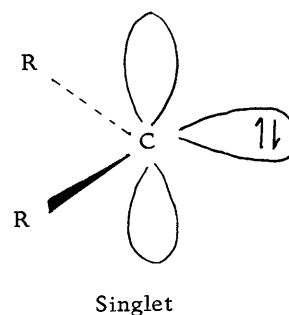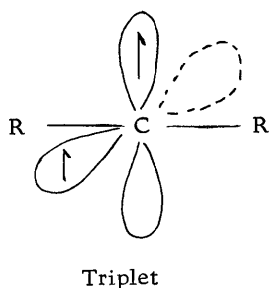
Evidence for the two spin states has been found in both

spectroscopy and chemical reactivity (72). Despite much work in this

area, the problem of how these two spin states behave has not been

fully solved. At least with methylene, and probably with dialkyl

carbenes, the reactive state is usually a singlet and the ground state

a triplet. The complex problem of triplet versus singlet carbenes

has been reviewed in detail (72).
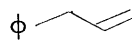
Electrophilic Character of Carbenes

Carbene intermediates, though neutral, are electron deficient and usually exhibit electrophilic properties. Their reactions with nucleophilic olefins to give cyclopropanes are characteristic. There are, however, some carbenes containing electron donating groups which react in a nucleophilic manner. Nucleophilic carbenes are exceptional and they will be discussed in a later section of this thesis.

Skell (120) demonstrated the electrophilicity of dibromocarbene through competition reactions of various olefins (Table 1). The electron seeking power of dibromocarbene was further shown by its close parallel to the relative reactivity of bromination and perbenzoic acid epoxidation. Similarly, competition studies by Doering (39), Closs (30) and Seyferth (110) have shown dichloromethylene and monochloromethylene to also be electrophilic. There is a noticeable decline of electrophilic property in the series $:CCl_2$, $:CHCl$, $:CH_2$.

In the area of central concern to this thesis, namely dialkylcarbenes, the opportunity for studying such competition reactions is quite limited. With these intermediates, intramolecular stabilization usually occurs much faster than intermolecular reaction. One of the few exceptions to this limitation are cyclopropylidenes $\underline{4}$.

Table 1. Relative Rates of CBr_2 Addition to Olefins.

Olefin	:CBr_2	Br+	Epoxidation
	3.5	2.5	very fast
	3.2	1.9	13.5
	1.0	1.0	1.0
	0.4	---	1.4
φ	0.02	---	0.02
	very slow	0.01	---
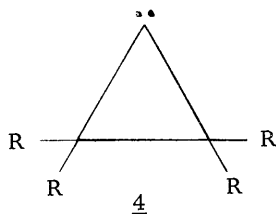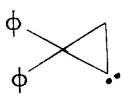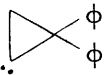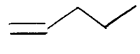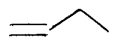
In this case, intermolecular reaction can compete with the intra-

molecular path. Jones et al. (68) have studied competition reactions

of 2,2-diphenylcyclopropylidene with various olefins (Table 2). This

dialkylcarbene, generated from base treatment of the corresponding

nitrosourea 5, behaved as an electrophile. The order of its relative

rates is in reasonable parallel with monochloromethylene consider-

ing the phenyl groups of the cyclopropylidene exhibit a dominating

steric effect.
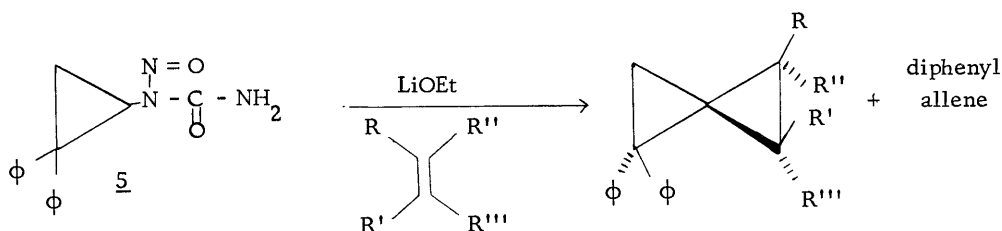
Jone's study indicates that dialkylcarbenes, which have no

unusual electron donating substituents, should behave as electrophiles

but the unusual bonding in cyclopropanes may change the character of

$R_2C:$. Studies of substituted cyclopropylidenes generated from

dibromocyclopropanes are clouded since it is difficult in these cases

to determine whether the attack on the double bond has occurred from

a free carbene or a "carbenoid complex." The existence of "carbenoid

complexes" is a general problem discussed below.

Table 2. Relative Rates of ϕ and :CHCl
Addition to Olefins.

Olefin	$\triangleright\!\!\!\!<^{\phi}_{\phi}$	:CHCl
	0.41	2.80
	1.00	1.00
	0.42	0.45
	1.15	0.91
	1.23	0.60
	---	0.23
	0.22	---

Carbenoid Reactions

An important route in the synthesis of cyclopropanes from
olefins is the α-elimination reaction of halogenomethyl derivatives
of zinc, lithium and other metals, for example, the Simmons-Smith
reaction leading to compound 7. The isolation of cyclopropane
derivatives is not definitive evidence for a carbene intermediate. In
many instances, it has been suggested that a "carbenoid complex"

(eg. 6 and 8) is formed from the olefin and the halogenomethyl

derivative. In order to account for the sterospecific addition in

these reactions, the carbenoid complex must afford the cyclopropane

in a one step manner rather than through an alternate two step

process. Specific examples of two such α-elimination reactions which

probably give cyclopropane derivatives via a "carbenoid complex" are

shown below.

$$CH_2I_2 + Zn/Cu \longrightarrow \quad \underset{6}{\ldots} \quad \xrightarrow{-ZnI_2} \quad \ldots \quad (117)$$

$$CH_2Br_2 + Li \longrightarrow \quad \underset{8}{\ldots} \quad \xrightarrow{-LiBr} \quad \ldots \quad (89)$$
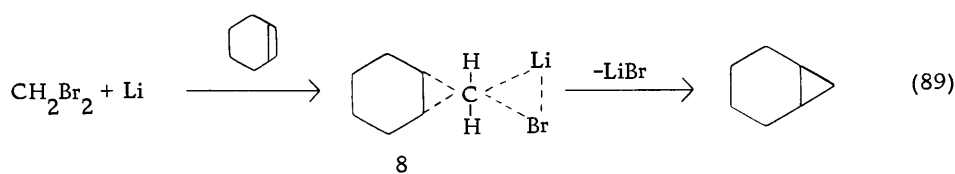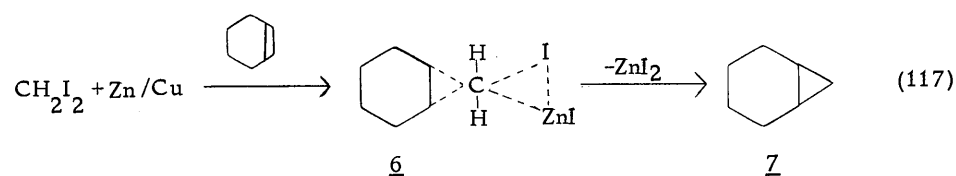
It is noteworthy that in these reactions no carbon-hydrogen insertion

products were observed as usually found with "free methylene."

Further evidence for "methylene carbenoid complexes" has been

reviewed (72).

Dialkylcarbenoid reactions were observed when secondary gem-

dibromo or gem-diiodo alkanes were treated with alkyllithium. The

intermediate halogenoalkyl derivative of the metal 9 has been isolated

in some cases (72), but it is not certain whether this intermediate

gives a "free carbene" 10 or acts as a "carbenoid species".

$$R\diagdown C \diagup X \qquad \xrightarrow[-RX]{RLi} \qquad R\diagdown C \diagup X \qquad \xrightarrow{-LiX} \qquad R\diagdown C: $$

with R, X groups; center carbon C; product **9** bearing Li; product **10**
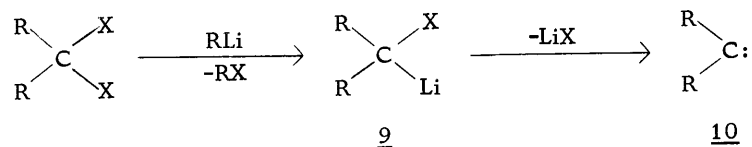
That dialkyl carbene formation can occur from these α-eliminations

is shown by comparing reactions (A) and (B) (71).

$(CH_3)_3C - CBr_2 - CH_3 \xrightarrow{MeLi}$ [cyclopropane] $+ (CH_3)_3C - C = CH_2$ (A)

65%   35%

$(CH_3)_3C - \overset{\overset{\text{N}_2}{\|}}{C} - CH_3 \xrightarrow{\Delta}$ [cyclopropane] $+ (CH_3)_3C - CH = CH_2$ (B)

55%   45%
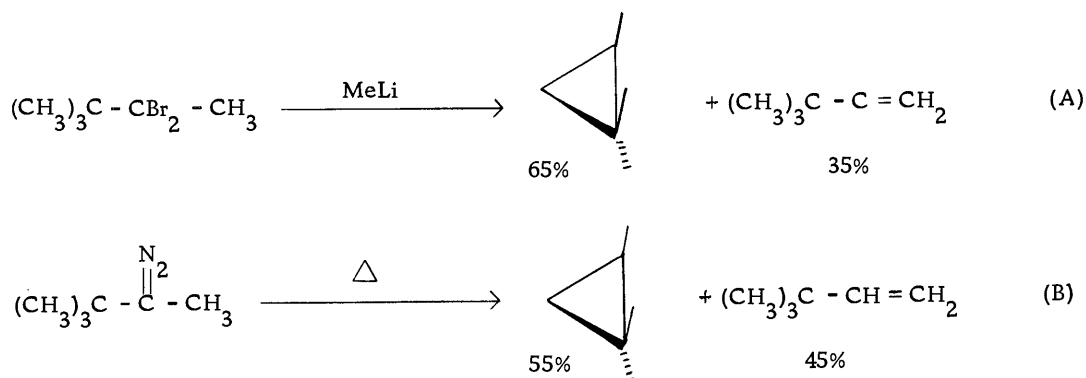
When α-eliminations of gem-dihalides are carried out in the

presence of olefins, the resulting cyclopropane derivatives may not

come about from addition of "free carbene". For example, diphenyl-

methylene obtained from the photolysis of diphenyldiazomethane 11

added to olefins non-stereospecifically (43). In contrast, the reactions

of dibromodiphenylmethane 12 with methyllithium gave cyclopropanes

stereospecifically (28). This difference in stereospecificity suggests

that these two reactions occurred through different mechanisms.
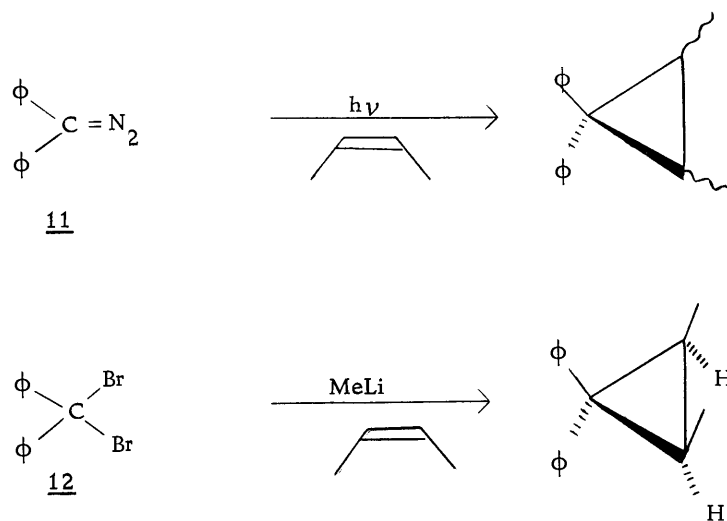
Cases in which the "carbenoid transition state" (eg. 6 and 8)

is not sterically possible, such as in 1,1-dibromocyclopropanes 13

and in 1,1-dihalo-2,2-alkylethylenes 14, may well proceed through

"free carbenes" (96). The exact mechanisms in such reactions have

not yet been elucidated.
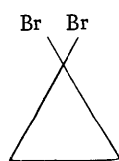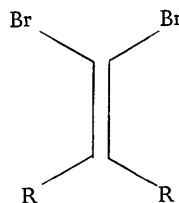
Formation of Dialkylcarbenes

Preparations of dialkylcarbenes may be classed in two broad

categories: 1) decomposition reactions, and 2) α-elimination

reactions. These methods are briefly outlined in Table 3. Methods

(C) through (F) have found more extensive use than the limited method

Table 3. Generation of Dialkylcarbenes.

(C) Hydrazones
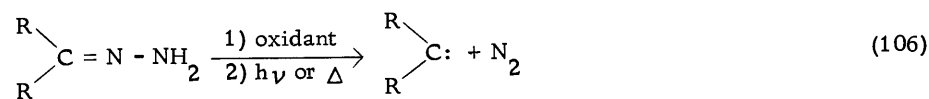
$$\underset{R}{\overset{R}{>}}C = N - NH_2 \quad \xrightarrow[\text{2) } h\nu \text{ or } \Delta]{\text{1) oxidant}} \quad \underset{R}{\overset{R}{>}}C: + N_2 \qquad (106)$$

(D) Toluenesulfonylhydrazones

$$\underset{R}{\overset{R}{>}}C = N - \overset{H}{\underset{}{N}} - Tos \quad \xrightarrow[\text{2) } \Delta \text{ or } h\nu]{\text{1) base}} \quad \underset{R}{\overset{R}{>}}C: + N_2 + M^{\oplus} \, {}^{\ominus}Tos \qquad (34, \ 70, \ 104)$$

(E) Diazirines

$$\underset{R}{\overset{R}{>}}C \overset{N}{\underset{N}{\|}} \quad \xrightarrow{\Delta \text{ or } h\nu} \quad \underset{R}{\overset{R}{>}}C: + N_2 \qquad (22, \ 54)$$

(F) Nitrosoureas

$$\underset{R}{\overset{R}{>}}\overset{H}{\underset{}{C}} - \overset{N=O}{\underset{}{N}} - \overset{O}{\underset{\|}{C}} - NH_2 \quad \xrightarrow[\text{2) } \Delta \text{ or } h\nu]{\text{1) base}} \quad \underset{R}{\overset{R}{>}}C: + N_2 + HO - \overset{O}{\underset{\|}{C}} - NH_2 \qquad (41, 68)$$

(G) Ketenes

$$\underset{R}{\overset{R}{>}}C = C = O \quad \xrightarrow{\Delta \text{ or } h\nu} \quad \underset{R}{\overset{R}{>}}C: + CO \qquad (20, \ 64)$$

(H) Gemdihalides

$$\underset{R}{\overset{R}{>}}\overset{X}{\underset{X}{C}} \quad \xrightarrow{MeLi} \quad \underset{R}{\overset{R}{>}}C: + RX + LiX \qquad (78, \ 92)$$

of ketene decomposition (G). The method of generating dialkyl

carbenes from gem-dihalides, (H), has been discussed in the

preceding section.
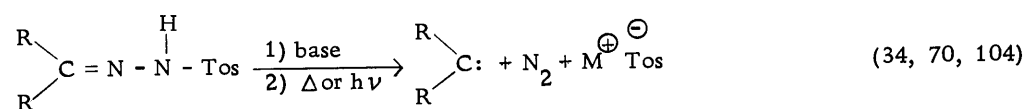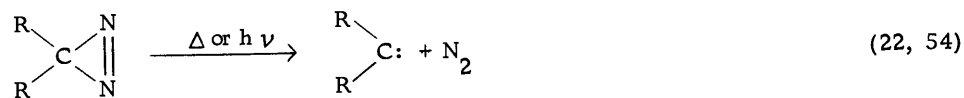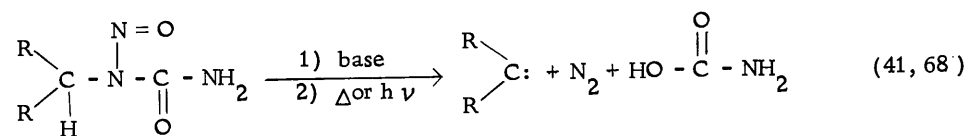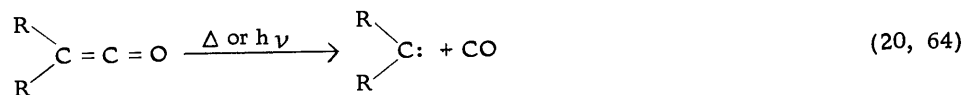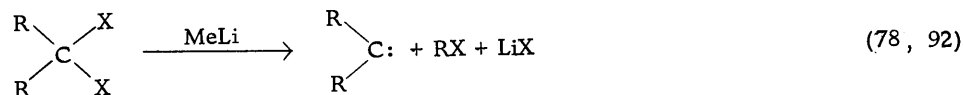
The methods of generating dialkylcarbenes shown in Table 3

have been carefully documented in the literature. Of these methods,

only base catalyzed decomposition of toluenesulfonylhydrazones

(tosylhydrazones) (D) is relevant to this thesis.

Bamford and Stevens (3) discovered in 1952 that pyrolytic

decomposition of tosylhydrazones with sodium in ethylene glycol

generated olefins. Shechter and Friedman (49) later found that by

changing to an aprotic medium that this decomposition could be

drastically changed. As shown in scheme 1, α-elimination of

toluenesulfinic acid generates a diazo compound which is protonated

by alcohols to give a carbonium ion and which loses nitrogen in

aprotic solvents to give a carbene (5).

Scheme 1

$$R_2C = N - \overset{H}{N} - Tos \xrightarrow{B:} R_2C = N - \overset{\ominus}{N} - Tos + BH^+$$

$$R_2C = \overset{\oplus}{N} = \overset{\ominus}{N} + Tos^{\ominus}$$

aprotic   protic

$$R_2C: + N_2$$

$$R_2\overset{\oplus}{C} - N \equiv N \longrightarrow R_2\overset{\oplus}{C} + N_2$$
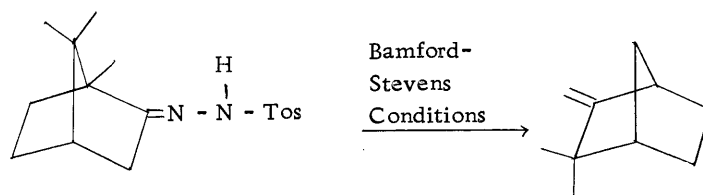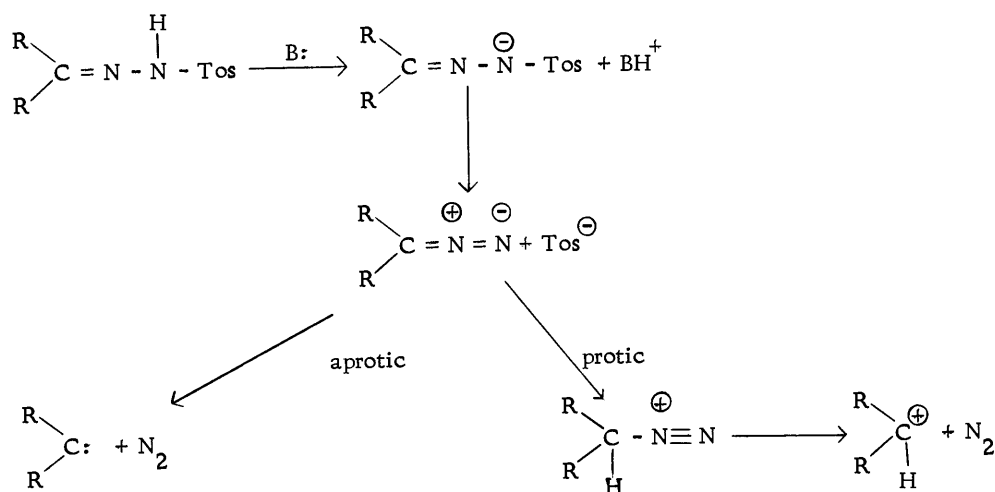
Lately it has been shown that this reaction is extremely

sensitive to base concentration (113, 114, 121). The most extensive

work in this area has been undertaken by Shapiro (113) who has studied

the effect of base concentration and solvent polarity on camphor

tosylhydrazone under "aprotic" conditions. The photolytic (34) and

pyrolytic (104) decomposition of camphor tosylhydrazone 15 had been

reported to give tricyclene 16 and camphene 17. Sharpiro

15   hν or Δ   16   17
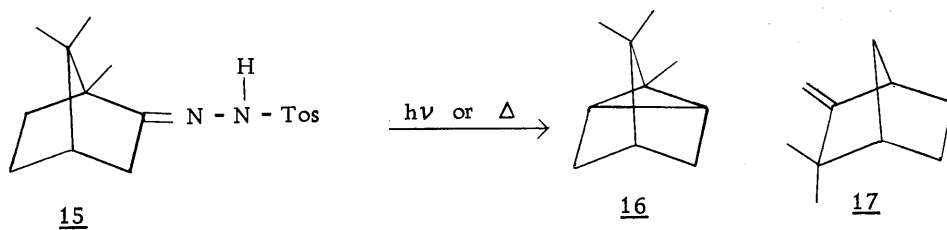
demonstrated that the relative amounts of tricyclene 16 and

camphene 17 were very dependent on base concentration and, to a

lesser degree, solvent polarity (Table 4).

Table 4. % Tricyclene[*] (NaOMe)

Solvent	0.25 eg.	0.50 eg.	0.75 eg.	1.0 eg.	1.25 eg.	1.50 eg.
DMF	23	24	24	36	45	84
Diglyme	40	41	43	60	84	97
Decalin	52	52	53	72	100	100

[*]remaining percentage is camphene

Table 4 shows low base concentration favored camphene

formation while high base concentration favored tricyclene to the

point where no camphene was formed. On the basis of the above

information, and data from deuterium incorporation studies, it has

been proposed that camphene arose from a carbonium ion whereas

tricyclene can be produced via a carbene and a poorly solvated

carbonium ion (Scheme 2). The increasing amount of camphene with

one equivalent or less of base was explained by postulating that the

excess tosylhydrazone acted as a proton donor to the intermediate

diazo compound.

The decomposition path of tosylhydrazones has been found to

be also dependent on the type of base employed. The pyrolysis of

pinacalone tosylhydrazone 18 with sodium hydride or sodamide gave

good yields of the least substituted olefin (74). On the other hand,

Scheme 2
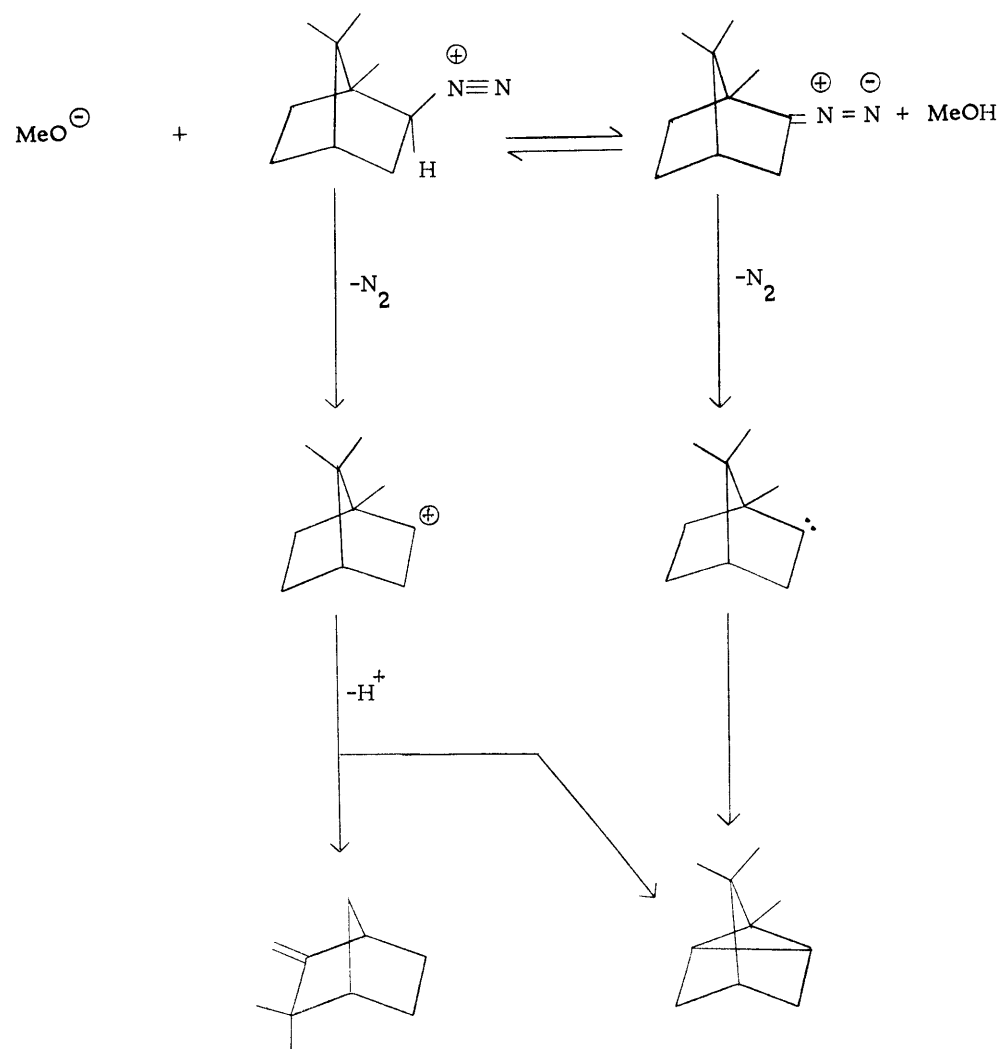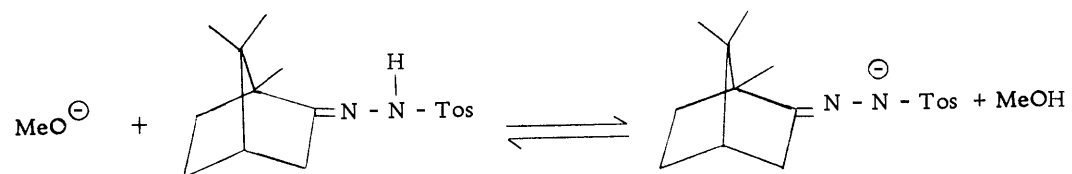
sodium methoxide and lithium hydride gave a majority of the

cyclopropane derivative (74) (Table 5). Treatment of pinacolone

tosylhydrazone with two equivalents of butyllithium also gave only

the least substituted olefin (70, 111, 115). When only one equivalent

of butyllithium was used, however, the reaction followed a carbenic

mechanism to give 1,1,2-trimethylcyclopropane (115) (Table 6). In

addition, α,β-unsaturated tosylhydrazones gave only dienes when

treated with sodium hydride or sodamide (74), but, when treated with

sodium methoxide, cyclopropenes were obtained (29). These results

are explained by the postulate that sodium methoxide and lithium

hydride generated carbenes, whereas sodium hydride, butyllithium,

and sodamide gave products derived through a carbanion mechanism

which is essentially that given in reaction (I) (70, 111, 115). The

sodamide-catalyzed decomposition of hexadeuteroacetone

tosylhydrazone 19 also supports such a mechanism (74).

19
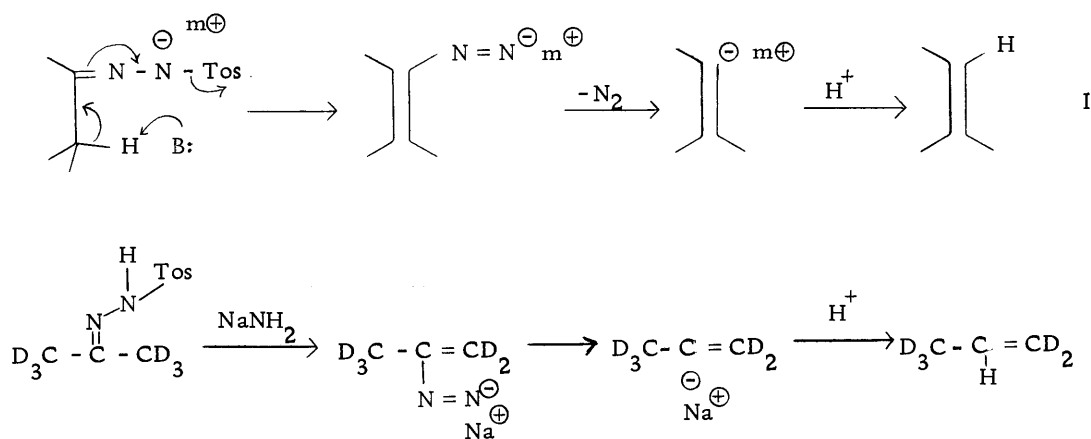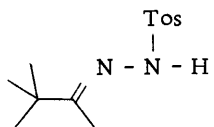
Table 5. Alkaline Decomposition of $\underset{\substack{| \\ N-N-H}}{\overset{\text{Tos}}{}}$ 18.
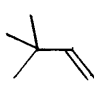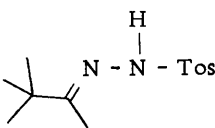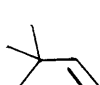
Product	NaOMe	LiH	NaH	NaNH$_2$
	41%	39%	80%	100%
	52%	40%	18%	---
	4%	13%	1%	---
	3%	8%	1%	---

Table 6. BuLi Treatment of $\underset{\substack{| \\ N-N-\text{Tos}}}{\overset{\text{H}}{}}$ 18.

Equiv. BuLi				
0.5	36%	11%	38%	18%
1.0	57%	40%	28%	13%
1.4	95%	5%	3%	
2.0	100%			

Reactions of Dialkylcarbenes

Due to their high reactivity, dialkylcarbenes normally react intramoleculecularly. It is this predominance of intramolecular reaction which distinguishes the dialkylcarbene from other carbenes. The intramolecular pathways available to dialkylcarbenes are: 1) insertion into carbon-hydrogen bonds, 2) addition to multiple bonds, and, 3) rearrangement. Only in cases where the dialkylcarbene has some stabilizing feature, or can lead only to a highly strained system by intramolecular reactions, do intermolecular reactions occur.

1) <u>Carbon-Hydrogen Insertion</u>: The most common carbon-hydrogen bond insertion products from dialkylcarbenes are olefins resulting from β-insertion (hydride shift) and cyclopropane formation from γ-insertion. In medium ring systems the close proximity of a carbon-hydrogen bond allows transannular insertion.

<u>β-insertion</u>:

$$-\overset{\displaystyle |}{\underset{\displaystyle |}{C}} - \overset{\displaystyle \overset{\textstyle H}{|}}{\underset{\displaystyle |}{C}} - \ddot{C} - R \longrightarrow -\overset{\displaystyle |}{\underset{\displaystyle |}{C}} - \overset{\displaystyle |}{\underset{\displaystyle |}{C}} = \overset{\textstyle H}{C} - R$$
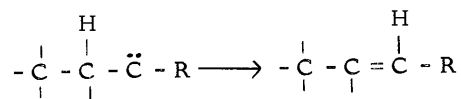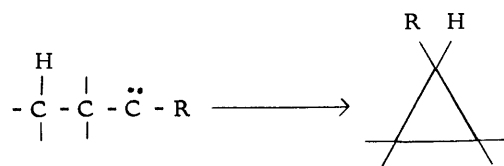
γ-insertion:

transannular insertion:
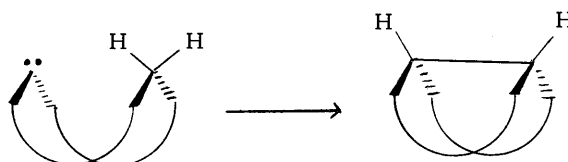
The direction of the β-insertion is normally selective for the hydrogen atom on the most highly substituted carbon (Table 7). The yields of cyclopropane derivatives from γ-insertion are dependent on the conformation of the molecule, or, put another way, on the distance of the carbon-hydrogen bond from the carbene intermediate (77). In aliphatic systems, the yields of cyclopropane increase with increased branching of the alkyl group.

In cyclic systems the relative amounts of β-, γ-, and trans-annular insertion are also dependent on the proximity of the carbon-hydrogen bonds to the carbene intermediate (Table 8).

2) _Addition_: Intramolecular insertion of dialkycarbenes is an expected reaction, but intramolecular addition to olefins is relatively uncommon. The relative yields of insertion products and addition products are influenced by the distance the double bond is removed from the carbene intermediate. Although α,β-unsaturated carbenes

provided good yields of cyclopropenes, other carbene intermediates

containing a double bond give only trace amounts of addition products.

Examples of alkenyl dialkylcarbenes are rare, but the products

expected from such intermediates might be deduced from the

examples of both alkyl- and dialkylcarbenes given in Table 9.

Table 7. β- vs. γ-Insertion (NaOMe).
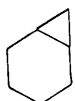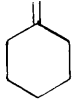
Tosylhydrazone	Products				
(CH₃)₃C–C=N–N-Tos with H, H	92%	7%	1%		(49)
(CH₃)₂CH–CH=N–N-Tos with H	38%	62%			(49)
CH₃–CH₂–C(CH₃)=N–N-Tos	0.5%	67%	28%	5%	(49)
cyclopentyl–C=N–N-Tos with H, H	72.5%	27.5%			(77)
cyclohexyl–C=N–N-Tos with H	8%	92%			(77)

(Note: structural drawings for the tosylhydrazones and product structures are represented as line structures in the original.)

Table 8. Cyclic Dialkylcarbenes.
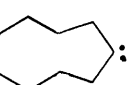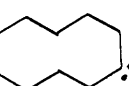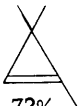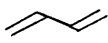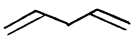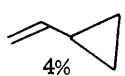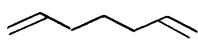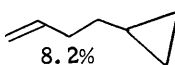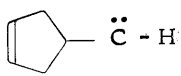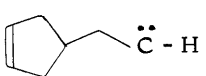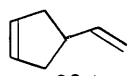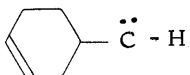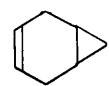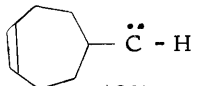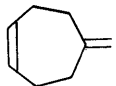
Ring System	β-insertion	γ-insertion	Transannular insertion
(51)	100%	---	---
(51)	100%	---	---
(97)	30%	70%	---
(51)	21%	79%	---
(51)	45%	9%	46%
(51)	22%	10%	66%
(51)	20%	---	80%

Table 9. Alkenyl Carbenes.

Carbene	Addition	β-Insertion	γ-Insertion
CH_3—C(=C(CH_3)(CH_3))—$\ddot{C}$—H (29), where left C bears CH_3 and CH_3	72%	—	—
CH_3=CH—CH_2—$\ddot{C}$—H (85)	16%	80%	—
CH_2=CH—$(CH_2)_2$—$\ddot{C}$—H (75)	—	96%	4%
CH_2=CH—$(CH_2)_4$—$\ddot{C}$—H (75)	1.9%	83.7%	8.2%
(cyclopentenyl)—$\ddot{C}$—H (86)	10%	52%	29%
(cyclopentenyl)—CH_2—$\ddot{C}$—H (109)	3%	30%	—
(cyclohexenyl)—$\ddot{C}$—H (2)	< 3%	35–70%	18–22% 15–30%
(cycloheptenyl)—$\ddot{C}$—H (109)	2%	< 15%	—

3) <u>Rearrangement</u>: Rearrangement reactions of dialkylcarbenes do not occur as readily as carbon-hydrogen insertion. Cyclopropylidenes, cyclopropylcarbenes, cyclobutylidenes and some neopentyl carbenes, however, are capable of migrating alkyl groups to give rearranged products. The major products from these carbene-types arise from rearrangement and these products are shown in Table 10.

Neopentyl carbonium ions give products resulting from carbon-skeleton rearrangement. In contrast, neopentyl carbenes give only a small amount of rearrangement compared to products arising from β- and γ-insertion (Table 11). The migration of phenyl groups, however, is more facile than that of alkyl groups.

Synthetic Utility of Dialkylcarbenes

The many examples discussed in illustrating the reactivity of dialkylcarbenes has already made evident the great synthetic potential of these intermediates. In addition to "normal" cyclopropane derivatives discussed earlier, the γ-insertion reaction has been used with success in the synthesis of many strained-ring compounds which would have been very difficult, if not impossible, to form by other methods (Table 12). Unfortunately, spirocyclopropane formation from dialkylcarbenes has been limited to cyclopropylidenes, cycloheptatrienylidene <u>33</u> and cyclopentadienylidene <u>36</u>. From a synthetic

Table 10. Cyclopropylidenes, Cyclopropyl Carbenes and Cyclo-
butylidenes.
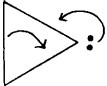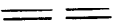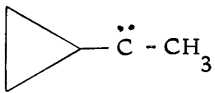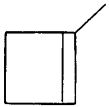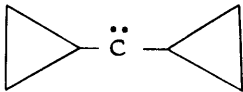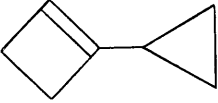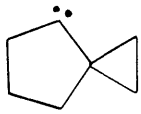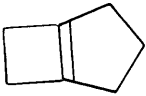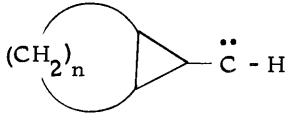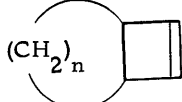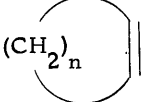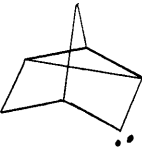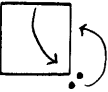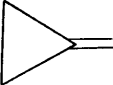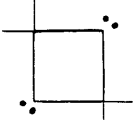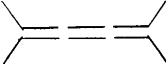
Carbene	Major Product

Cyclopropylidenes:

(68, 92)

Cyclopropyl Carbenes:

(50)

(9)

(10)

(76)

(83, 32)

Cyclobutylidenes:

(50)

(8)

Table 11. Neopentyl Carbenes.

CH₃—C(CH₃)₂—C̈—H

7%   1%   92%   (49)

φ—C(CH₃)₂—C̈—H
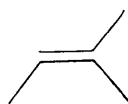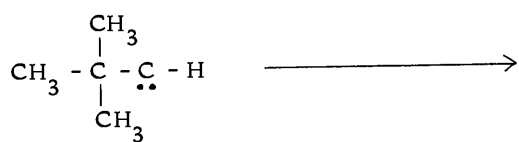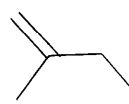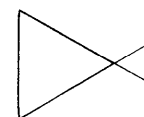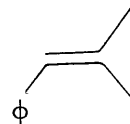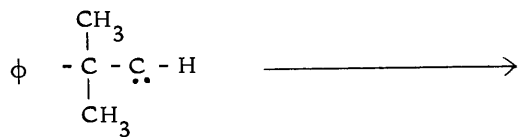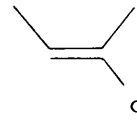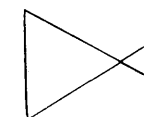
51%   9%   40%   (102)
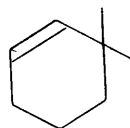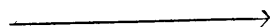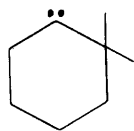
100%   (80)
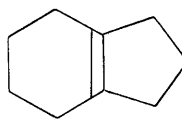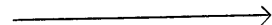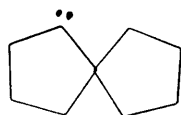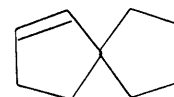
12%   53%   32%   (80)

point of view, it would be very interesting if other dialkylcarbenes

could be found which were also capable of forming spirocyclopropanes.

In this study of steroid carbene reactions, several carbenes were

found which did have the surprising capacity to form many fascinating

spirocyclopropane derivatives from intermolecular addition to olefins.

Table 12. Strained Ring Compounds from R_2C:
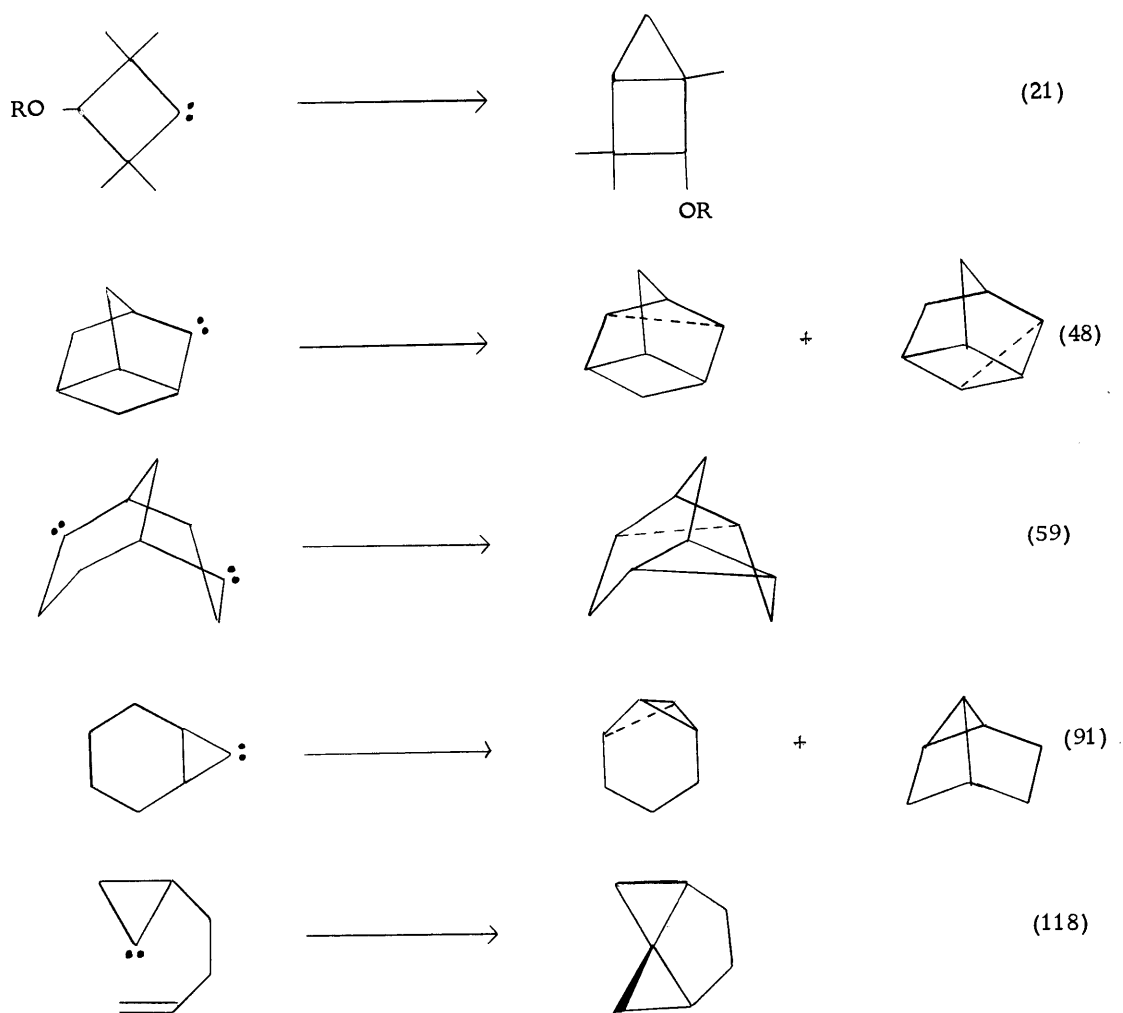
The use of dialkylcarbenes in synthesizing strained olefins such as vinylcyclopropanes, cyclobutenes, cyclopropenes, and allenes has been shown in Table 10. The ability of dialkylcarbenes to give the more stable olefin by β-insertion has been pointed out, and this synthetic potential is well illustrated in the next section "Steroid Carbene Reactions" (Table 15). The usefulness of a carbene in olefin synthesis lies not only in its selectivity, but also in its ability to avoid carbonium ion-type rearrangements. For example, dialkyl carbenes have been used to introduce double bonds in neopentyl positions 20 and in bicyclic compounds such as 21 without causing rearrangement. In this thesis β-hydrogen insertion reactions from carbenes such as 22 have been used to generate sensitive dienes which cannot be prepared easily by traditional routes.

20   (80)

21   (1)

22
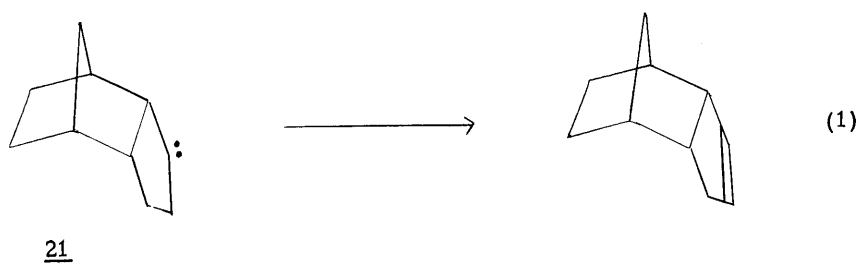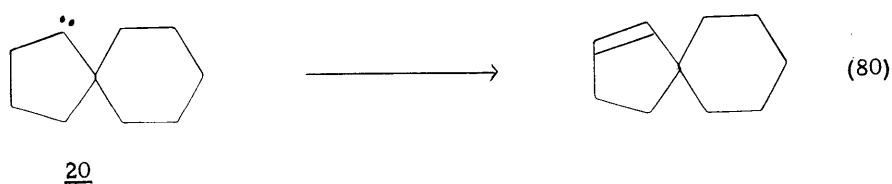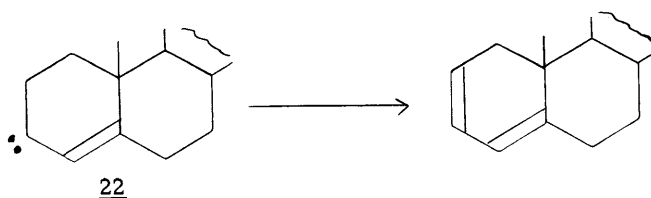
Stabilized Carbenes

Intermolecular reactions are the least likely of any of the reactions of the R_2C: intermediate. Methylcarbene 23 and dimethyl-carbene 24 should be among the more stable dialkylcarbenes since the ease of hydrogen shift follows the order

$$CH_3 - \overset{..}{C} - H \qquad\qquad CH_3 \overset{\overset{..}{C}}{\diagup} CH_3$$

23   24
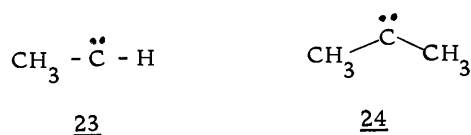
tertiary > secondary > primary. In fact, low yields of addition products (approximately 5%) have been formed from methyl carbene with olefins such as cyclohexene (47) and propene (53). On the other hand, dimethyl carbene gave no addition products with olefins (54).

It can be imagined that dialkylcarbenes which can't be readily stabilized by "hydride shift" or γ-insertion might very well react intermolecularly. One such system, 2,2-diphenylcyclopropylidene, has been discussed already. Another cyclopropylidene derivative, which is incapable of forming an allene, has been generated from 7,7-dibromonorcarane 25. This carbene reacted intermolecularly with ether solvent to give the insertion product 26 (76). In the

presence of cyclohexene, the spiro compound <u>27</u> was isolated along

with dimer <u>28</u> (90). The literature is devoid of other examples of
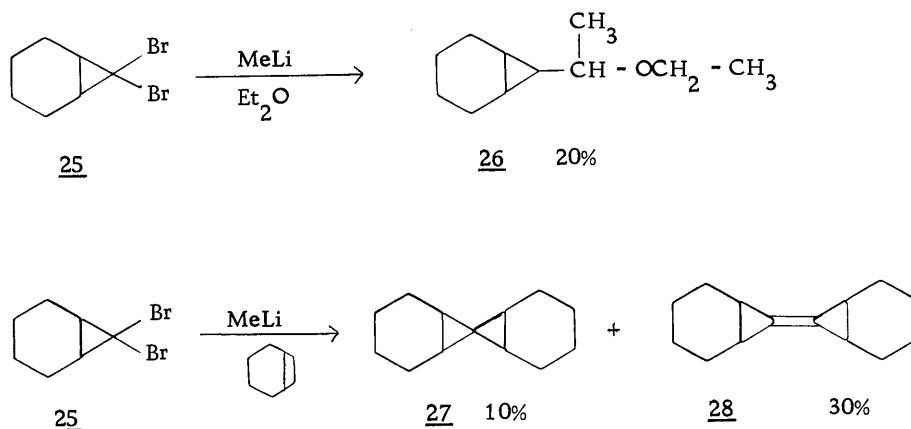
carbenes which contain β-hydrogens and still react intermolecularly

with the solvent rather than undergoing intramolecular carbon-

hydrogen insertion or rearrangement.

The carbene intermediate, which is by nature electrophilic,

may be changed to increasing nucleophilicity and increasing stability

by changing the adjacent groups to stronger electron donors (K). For

example, the pyrolysis of sodium salt <u>29</u> gives no adduct with the
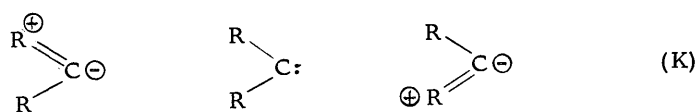
nucleophilic olefin cyclohexene but does add to the electrophilic

olefin diethyl maleate (31). Carbene intermediates having adjacent

No adduct

ϕ

MeO — C = N - N - Tos with H below N

29

EtOOC / COOEt

MeO, CO$_2$Et, CO$_2$Et, ϕ structure

CH$_3$O, CH$_3$O — C:

30

CH$_3$S, CH$_3$S — C:

31

ϕ — N, N — ϕ ring with :

32
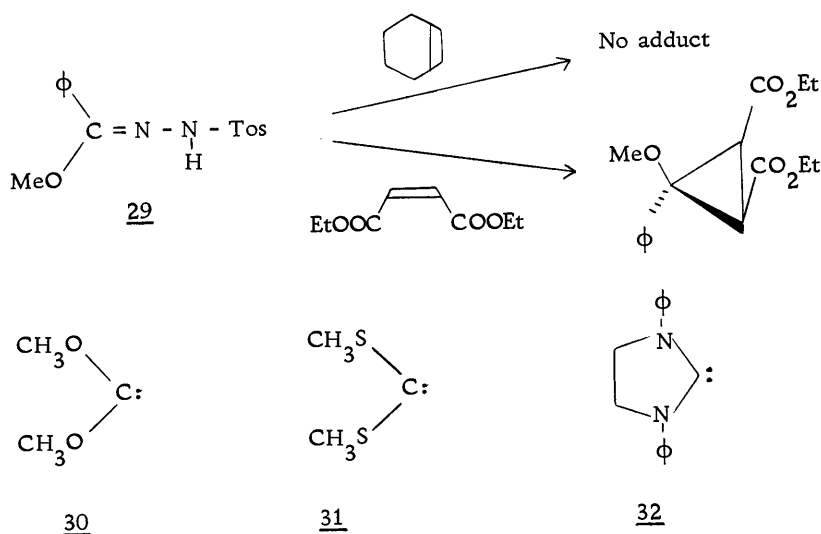
electron donating hetero atoms, such as 30, 31, and 32, form dimers

readily (82, 84, 125). Dimer formation and the lack of reactivity

with alkenes are characteristic of such carbene intermediates.

It is conceivable that unsaturated systems might also stabilize

a carbene in a similar, but less pronounced, manner. Such unsatura-

tion, as shown in Table 13, could stabilize an intermediate carbene

through electron donation and delocalization.

Cycloheptatrienylidene 33 has recently been generated from

the corresponding tosylhydrazone (67, 95). In the presence of

nucleophilic olefins, such as cyclohexene, only dimer 34 was

isolated. In contrast, when 33 was generated in the presence of

electrophilic olefins, dimethyl fumarate or dimethyl maleate,

spirononatriene 35 was produced.. The formation of the trans-

isomer in both cases is indicative that a diradial intermediate is

involved. Though the possibility of an intermediate pyrazoline

precluding the formation of spirononatriene _33_ has not been

rigorously excluded, the products formed are those expected from

a carbene of high nucleophilicity.

Table 13. Stable Dialkylcarbenes.
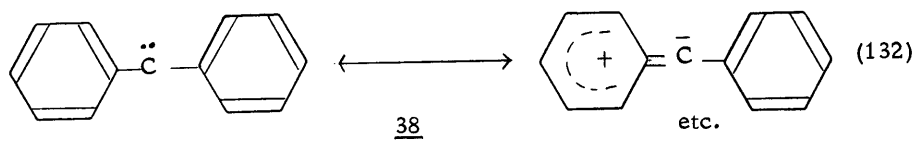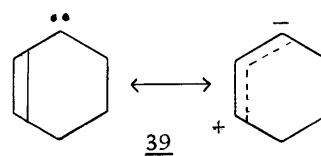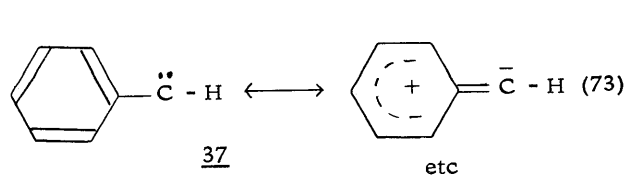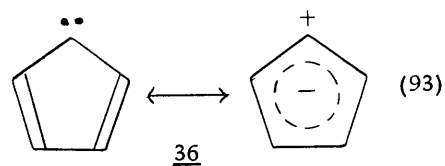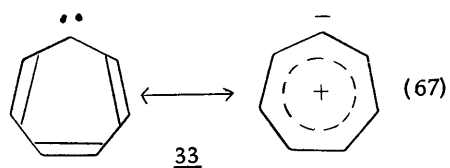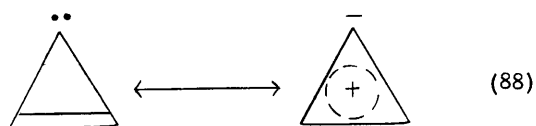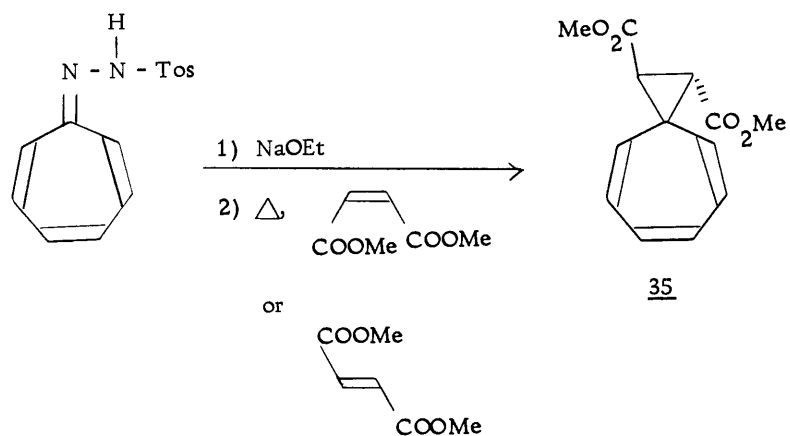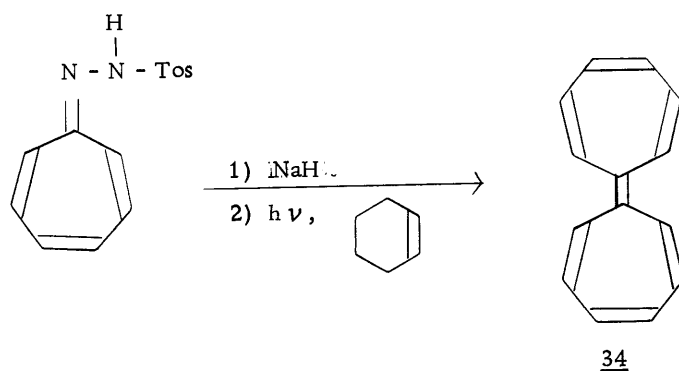
Cyclopentadienylidene 36 did not demonstrate the anticipated strong electrophilicity in competition studies, but it did readily add to nucleophilic olefins when steric factors were not overriding (93). Also, in contrast to cycloheptatrienylidene 33, carbon hydrogen insertion products were observed and no dimeric products were reported (L).
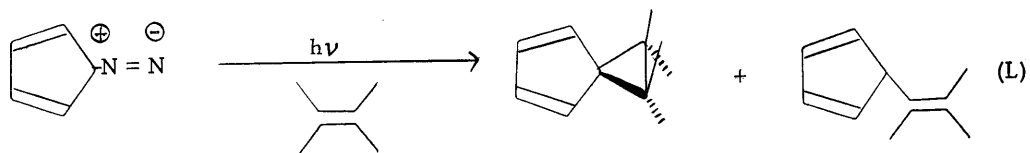
Phenylmethylene _37_ and diphenylmethylene _38_ show unusual stability. Both systems add to olefins, but in many solvents dimer formation is the more predominant of the two processes. The ground state of each system is a triplet and their carbon-hydrogen insertion reactions often resemble those of radicals. Although phenyl- and diphenylmethylene might be expected to be nucleophilic, only diphenylmethylene has been established as having this property (73). Aryl- and diarylcarbene chemistry has been extensively studied and a review is available (71).

From the limited studies that have been made on stabilized dialkylcarbenes, some general patterns emerge which might be used to determine whether a particular carbene is nucleophilic or electrophilic. Typically, a nucleophilic carbene would be expected to form a dimer in the presence of nucleophilic olefins and to form an addition product with electrophilic double bonds. An electrophilic carbene, on the other hand, should form addition products with nucleophilic olefins and, in their absence, insert into carbon-hydrogen bonds. Dimer formation from a cyclopentadienylidene was not observed even in carbontetrachloride (71, 87), but was found only when fluoroethers were used as solvent (35). There is, of course, a spectrum of electrophilic behavior (cyclopentadienylidene) to nucleophilic character (cycloheptatrienylidene).

The previously discussed stable carbenes, due to their

structural features, must react intermolecularly. In contrast, a

cyclic β-alkenyl carbene such as 39, may react intramolecularly or

if the intermediate is sufficiently stabilized it could conceivably

react intermolecularly. Since cyclic β-alkenyl carbenes can't

react with the adjacent double bond, it is possible that they might be

stabilized by delocalization of the π -electrons. This type of

stabilization would be similar to that observed in keto- and

carbalkoxycarbenes, 40 and 41, which often react intermolecularly (71).
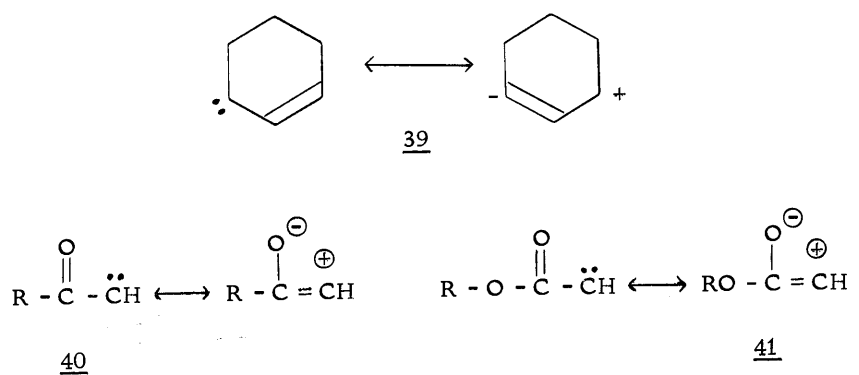
Only two cyclic systems containing β-alkenyl carbenes have been

investigated. These systems, 42 and 43 (discussed in a later

section), reacted intramolecularly. The carbene intermediates 42

and 43 have certain features which might cause them to be atypical,

and it was not at all clear that the methods chosen actually generated

free carbenes. Indeed, in the course of this work, it has been found

AcO

42   43
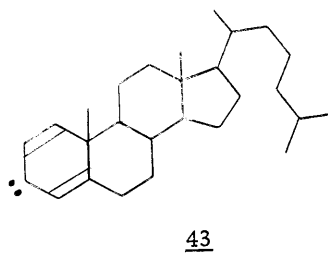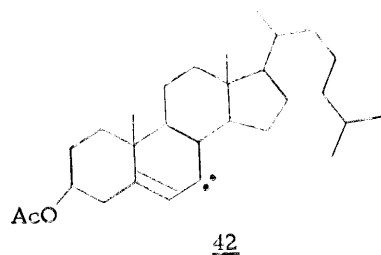
that cyclic β-alkenyl carbenes show reactivities quite different from

their saturated analogs.

Stable Carbenes From Tosylhydrazones

Stable carbenes generated from tosylhydrazones do not always

give the usual carbenic products such as intramolecular stabilization,

attack on solvent, or dimerization. One of the alternate pathways

involves formation of azine 44. While azine formation need not result

from stable carbenes, it is quite often observed under these condi-

tions. The exact mode of formation of this product has not been

determined. Azines could result from intermolecular attack of the

carbene on the diazo intermediate (132) or on the tosylhydrazone

salt (21, 79). Nucleophilic displacement between two diazo com-

pounds could also give 44 (52). There are several other ways in
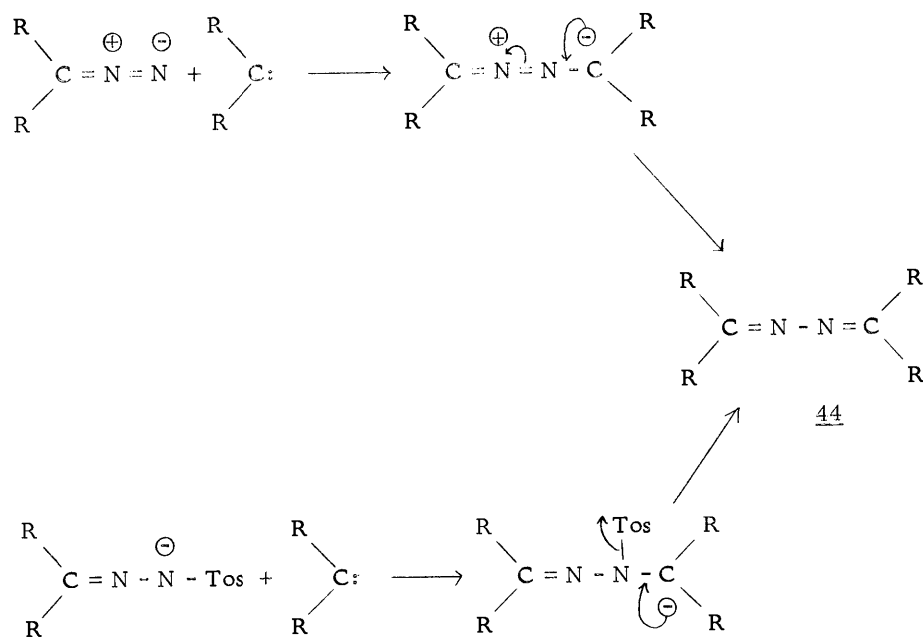
which azines may be formed without invoking an intermediate carbene.

Aside from azine formation, there are several products which are formed only when tosylhydrazones give carbenes which cannot readily undergo the usual processes of intramolecular stabilization (Table 14). These unusual products are p-tolylsulfones 45, p-tolylsulfinates 46 and N-alkyl-tosylhydrazones 47.
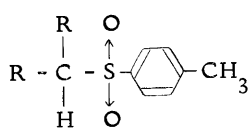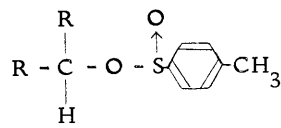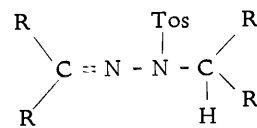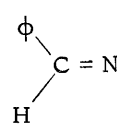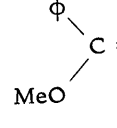
45   46   47

Table 14. Polar Products From Tosylhydrazones.

Tosylhydrazone		Excess Base		Excess Tosylhydrazone		Attack on Solvent
		Sulfone	Azine	N-Tosylate	Sulfinate	
N - N - Tos	(83)	30-50%	4%	52%	---	none
H-C = N -N - Tos	(126)	---	---	Present	42%	none
φ—C = N - N - Tos / H	(99)	3%	13-33%	41%	---	10%
φ—C = N - N - Tos / MeO	(31)	3-17%	12-46%	---	---	electrophilic olefins only

Yields of sulfones in such decompositions are highest under extremely aprotic conditions (83). It is believed that a carbene, rather than a carbonium ion, captures the sulfinate anion giving the reasonably stable sulfone anion which is then protonated on work-up (M). Wilt (126) has argued that the ambident nucleophile (sulfinate anion) should react at its oxygen atom with a carbonium ion, but with a neutral carbene at its sulfur atom.

$$\text{(M)}$$

$$\text{(N)}$$
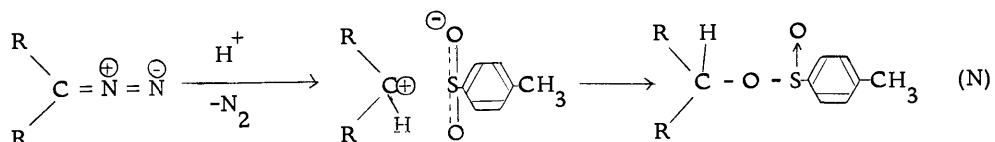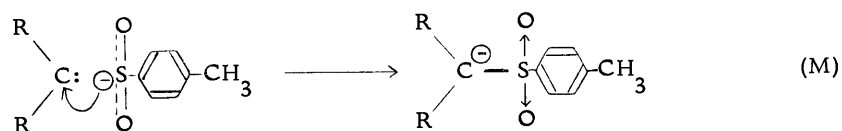
If less than one equivalent of base is used, or if only part of

the tosylhydrazone is converted to its anion, stable carbenes may

undergo a different mode of reaction to give N-tosylates $\underline{47}$, and in

some cases, sulfinates $\underline{46}$ (99). The sulfinate may be explained by

assuming the free tosylhydrazone acts a proton donor affording a

carbonium ion. The carbonium ion could then react with the oxygen

atom of the sulfinate anion (N). The sulfinates thus formed are

readily cleaved under mild conditions to give alcohols. The N-

tosylates $\underline{47}$ may come from intermolecular insertion of the carbene

into the nitrogen-hydrogen bond of the excess tosylhydrazone (O)

(83, 126).

$$\text{(O)}$$
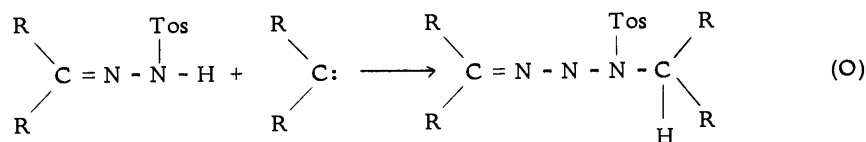
Besides the polar products described thus far, carbonyl compounds may be isolated in low yields from some reactions (99). The proposed mechanism allows the oxygen atom of the sulfinate anion to attack the carbene (P).

$$\underset{R}{\overset{R}{>}}C: \overset{O}{\underset{O}{\overset{|}{S}}}\!\!\left\langle\bigcirc\right\rangle\!\!-CH_3 \longrightarrow \underset{R}{\overset{R}{>}}C-O-\overset{\downarrow}{\underset{O}{S}}\!\!\left\langle\bigcirc\right\rangle\!\!-CH_3 \longrightarrow \underset{R}{\overset{R}{>}}C=O \qquad (P)$$
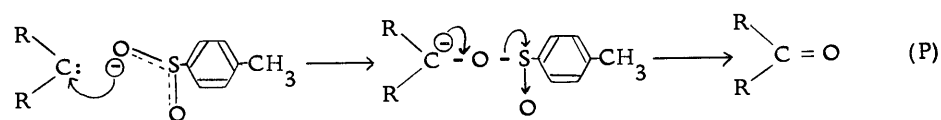
Steroid Carbene Reactions

Within the area of steroid chemistry, extensive effort is aimed at modifying a given structure in the hope of increasing some positive biological activity while, at the same time, eliminating undesirable side effects. Steroid carbene reactions seemed an attractive area to study since they should provide a synthesis of "strained ring" steroids of potential biological interest. In addition, this type of reaction might also provide a simple synthesis of biologically active olefinic steroids. Furthermore, the rigid framework of the steroid nucleus is well suited to a stereochemical study of carbene reactions.

Surprisingly, when this work was begun, no reports of steroid carbenes had been made. Recently, Caglioti et al. (14, 15) have studied carbenes as a method of synthesizing steroid olefins (Table 15). These steroid carbene reactions are noteworthy for their specificity in "hydride shift", 48 - 53, and as potential methods of

Table 15. Steroid Carbene Reactions (15, 16).
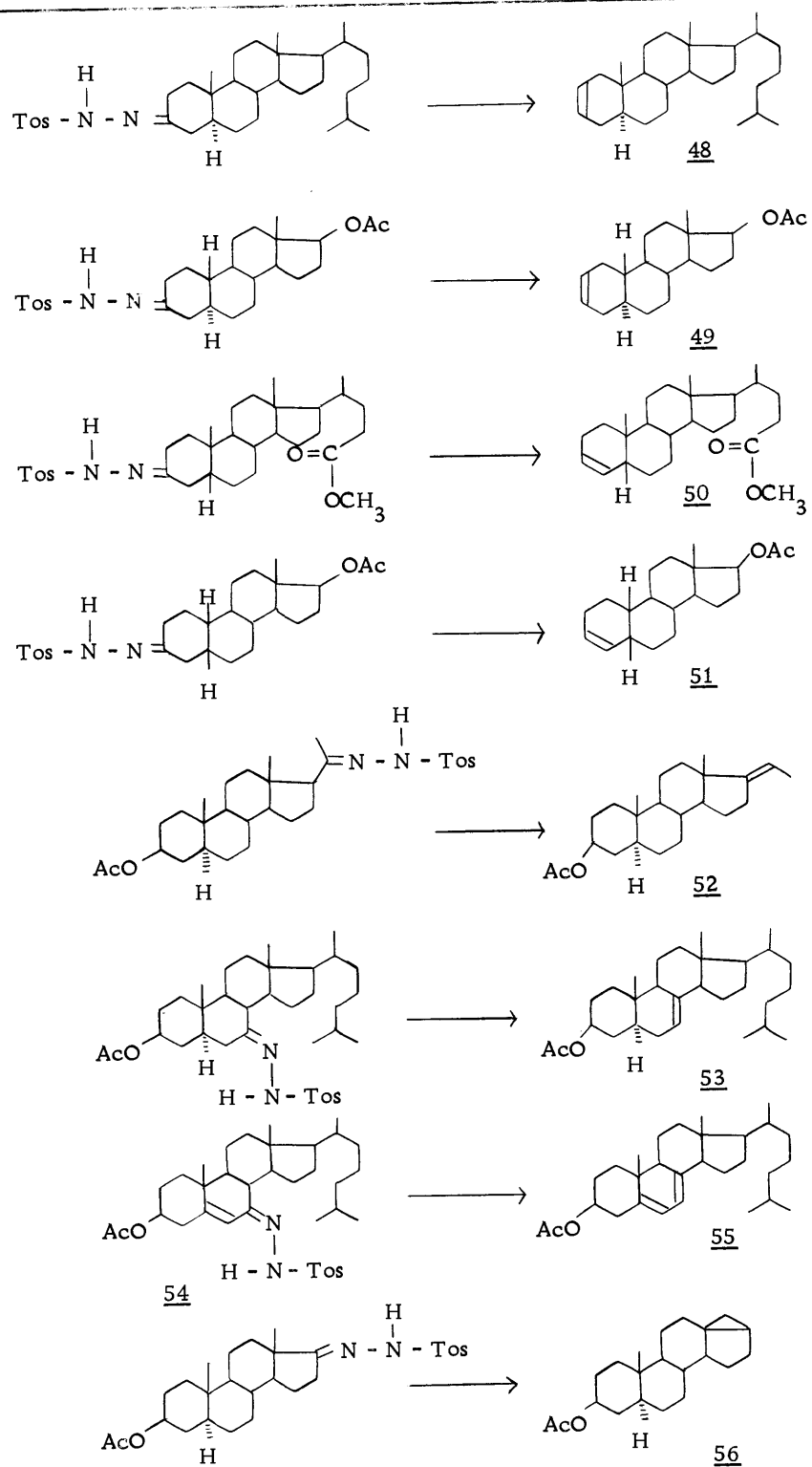
forming sensitive steroid dienes 55 and 18-activated steroids 56.

The reaction conditions used in this work were quite unusual in that

toluene, rather than diglyme, was used as solvent and sodium hydride

was used as the base.

Curiously, Caglioti (16) reported the preparation of 4-

cholesten-3-one tosylhydrazone 57 and 1-cholesten-3-one tosyl-

hydrazone 58 but did not report their carbenic decompositions. In

this thesis, these two tosylhydrazones have been studied and have

shown unexpected and extremely interesting properties.
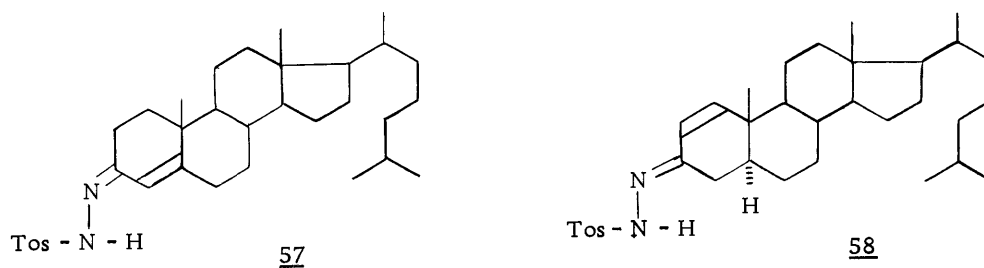
The only α,β-unsaturated steroid tosylhydrazone, other than 54,

which has been decomposed under carbenic conditions is 1,4-

cholestadiene-3-one tosylhydrazone 59. This intriguing system

decomposed to two 19-nor steroids 60 and 61 (33).
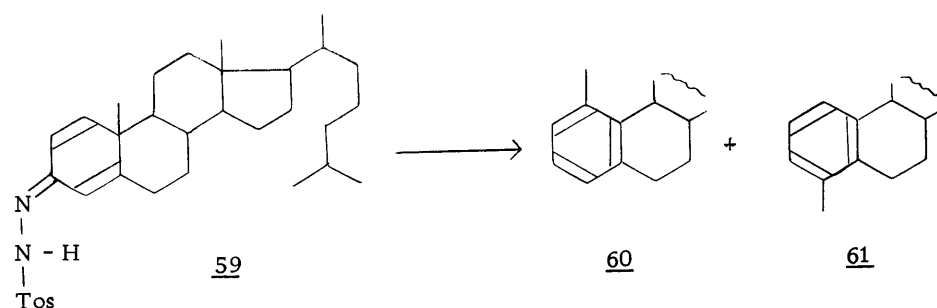
The proposed mechanism to 60 and 61 is based upon resonance

stabilization of the carbene.
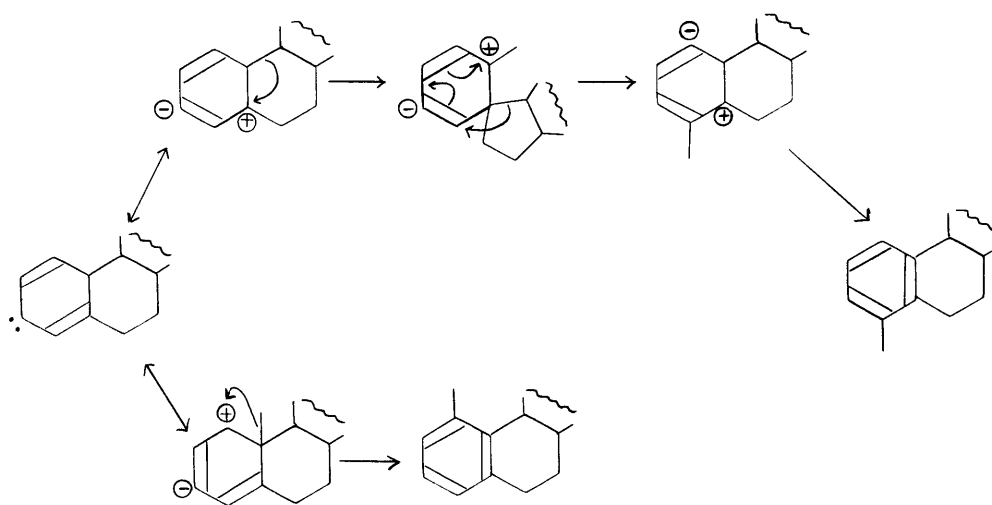
Decomposition of diazirines as a method of generating

steroidal carbenes has been limited by the steric and electronic

restrictions in their synthesis (22). 3, 3-Aza-5α-androstane-17β-

ol-17-acetate 62 has been pyrolyzed to give, in agreement with

Caglioti's results, a single isomer, 5α-androst-2-ene-17β-ol-17-

acetate 63.
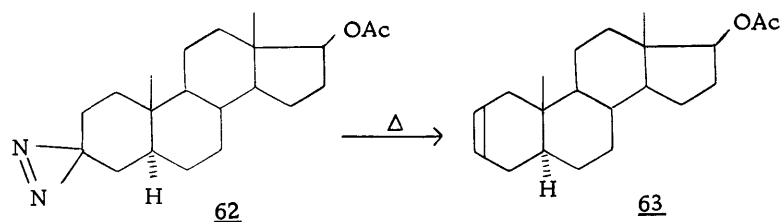
Steroid tosylhydrazones have been used in ways other than as

carbene precursors. Under Bamford-Stevens conditions, tosyl-

hydrazones have been used for synthesizing steroid olefins. Typical

of this reaction is the treatment of a 17-keto tosylhydrazone $\underline{64}$ with

sodium in ethylene glycol (66). Also, treatment of some steroid
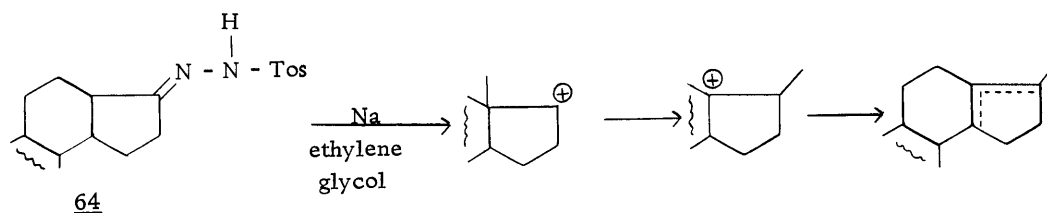
tosylhydrazones with sodium borohydride or lithium aluminum

hydride provides a mild method of reduction to saturated carbon (13,

16, 17). The mechanism of this reaction has been studied by

Djerassi et al. (45).

Steroid Justification

It was of interest to investigate steroid carbenes for both synthetic and stereochemical reasons. From a synthetic point of view, carbenes might provide a simple one-step synthesis of small ring steroid compounds and other strained systems. The steroid nucleus was also attractive for investigating conformational factors in carbene reactions. This rigid system seemed excellent for studying the stereochemical requirements for both β- and γ-carbon-hydrogen insertion and intramolecular addition.

If the carbene route proved effective, a study of the biologically interesting compounds could be made. In this light, a justification of this work from a biochemical point of view is discussed below.

The immense importance of the α,β-unsaturated-3-one system in ring A can be readily appreciated when one considers that all of the naturally occurring hormones contain this common feature (eg. 65, 66, 67). Early workers in the steroid field observed that removal

65   66   67
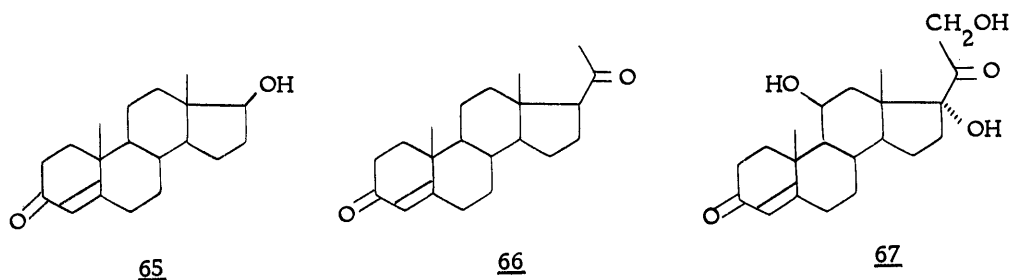
of the oxygen function to saturated carbon left the hormones without

activity (11). For a long time, it was believed a carbonyl or

oxidizable alcohol function at C-3 was needed for biological activity.

During this period, steroid chemists were concerned with modifying

hormones such as testosterone 65, progesterone 66, and cortisol 67

through the introduction of new functional groups in various positions

of the steroid nucleus. In 1959, however, 17-alkylated-3-deoxo-19-

nortestosterones (eq. 68) were found to be powerful progestational

agents (36) and thus showed that the presence of an oxygen atom at

C-3 was not necessary for biological activity. From this work evolved
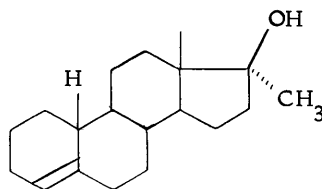
68

the idea that the electron density pattern of the A-ring was the real

source of biological activity. Various monoolefins containing the

Δ^1, Δ^2, Δ^3 and Δ^4 double bonds were synthesized and were found to

show varying amounts of biological activity (11).

Syntex workers (6) thought introduction of more than one SP^2

hybridized carbon atom into ring A would flatten the ring and make

it easier for the steroid to fit onto an enzyme receptor surface.

These workers developed the methods outlined below for forming the

sensitive 2,4- and 1,3-steroidal dienes, 69 and 70, respectively.

2,4-dienes:
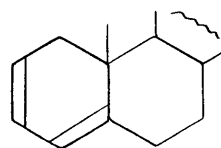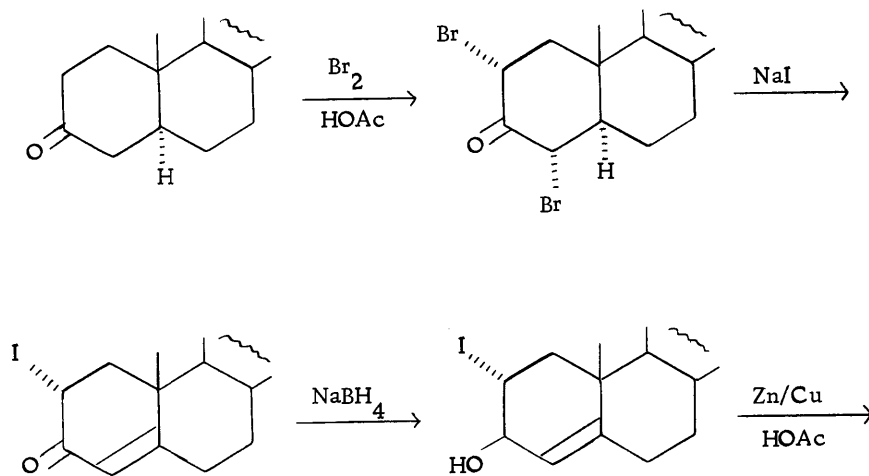
69

1,3-dienes:
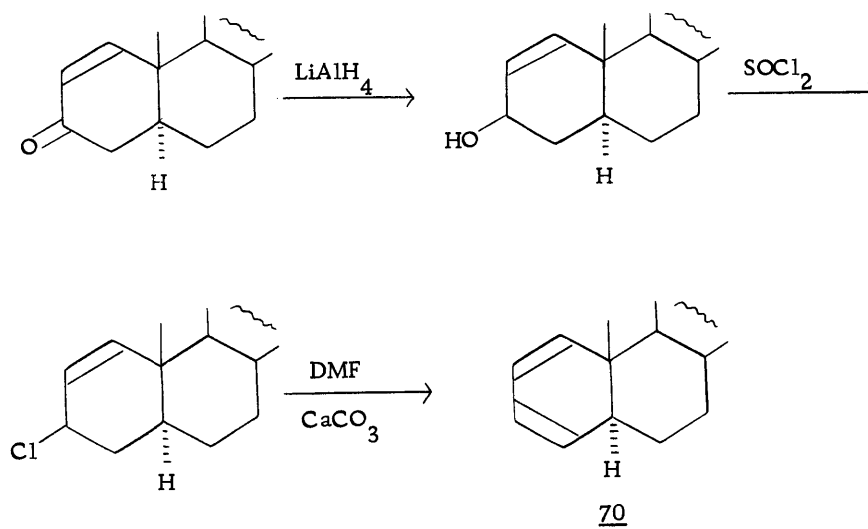
70

In this work, it seemed that, since the α,β-unsaturated ketones were readily available, a superior and more direct route to these A ring dienes would be decomposition of the appropriate α,β-unsaturated tosylhydrazones.

The requirement of high electron density in the A-ring has further been tested by introduction of a cyclopropane ring 71 (129). The cyclopropyl grouping, in which three regions of high electron density lie outside the triangle of carbon atoms, has endowed several steroid systems with biological activity (129). Cyclopropyl steroids,

71   72   73
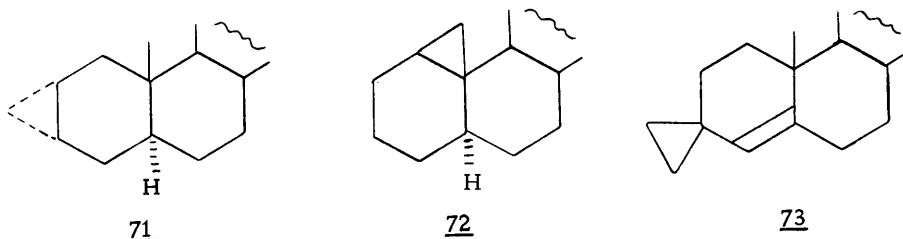
of the type exemplified by 71, have become accessible through the addition of the Simmons-Smith reagent, dihalo carbenes, or diazo-methane to unsaturated positions. Cyclosteroids similar to 72 and 73, which have been synthesized in this work, are relatively uncommon and should be of potential biological interest.

During the course of this work it was discovered that steroid carbenes could also serve for the introduction of halogenated carbons. Such introduction of halo atoms into steroids is particularly valuable since these substituents (eg. 9α-F, 6α-Cl, 16α-Cl, 2α-Cl) often

impart favorable activity to the steroid (46).

Also, in the course of this work, the formation of steroid pyrazoles from tosylhydrazones was observed. Recently it has been reported that such steroid derivatives can reduce undesirable biological activity of the parent steroid while retaining the desirable effects (26, 107, 108). For example, pyrazole 74 was synthesized

74
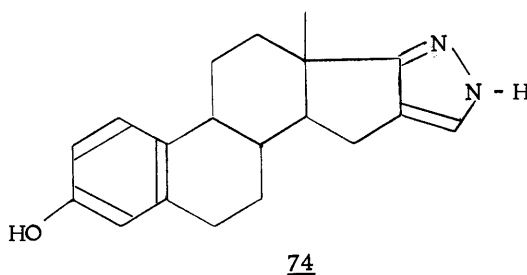
for the purpose of retaining the useful activity of estradiol while destroying the feminizing properties. Although many of the reactions in this thesis were discovered by chance, they should prove to be quite valuable and further document the synthetic utility of carbenes.

RESULTS AND DISCUSSION

The primary objectives of this work were to investigate

dialkylcarbenes as a means of carrying out steroid transformations,

and simultaneously, to study the nature of these intermediates.

Systems were chosen in which carbenes would hopefully serve as

useful synthetic intermediates, but which would also shed some light

on the characteristics of these species.

75   76   77
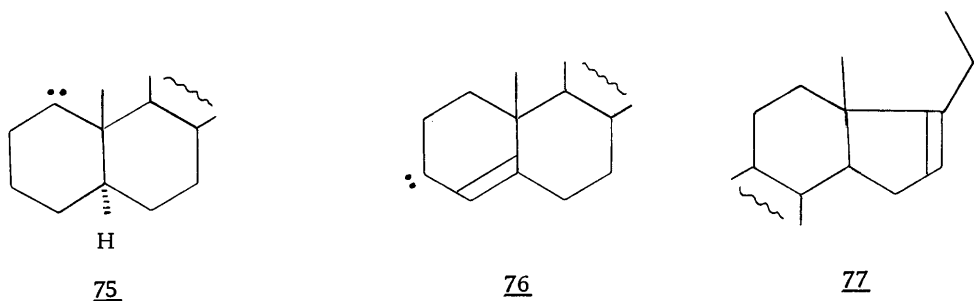
The types of steroid carbenes which were investigated are

exemplified by 75, 76 and 77, in which there exists either a pos-

sibility of forming a strained cyclosteroid or a strained steroid diene.

It has already been pointed out that such products might show

biological activity. Of particular interest was the degree of

stability imparted by a double bond in conjugation with the electron

deficient carbon as in 76.

Cyclization onto the C-18 and C-19 Methyl Groups

Cyclization onto C-18. The 17-keto tosylhydrazone 78 was

selected for the initial work. Tosylhydrazone 78 was especially

attrative since either γ-insertion or "hydride shift" stabilization of

the carbene intermediate would produce a steroid for which available

methods were laborious or gave low yields. The γ-insertion route

was of particular interest since this would provide a facile synthesis

of a 13β,17β-methylene steroid 79. The only previous route to such

cyclosteroids proceeded in very low yields (62).
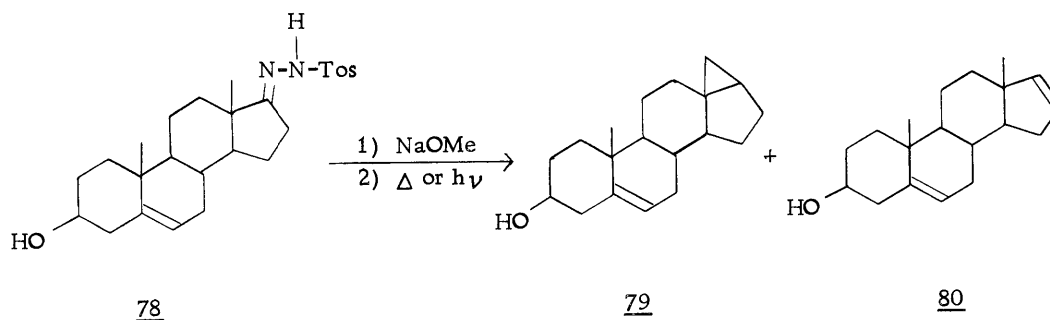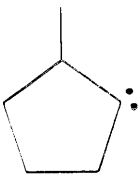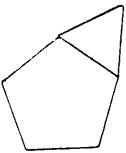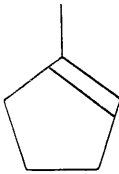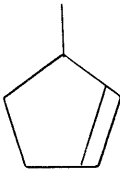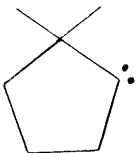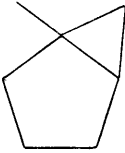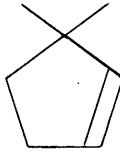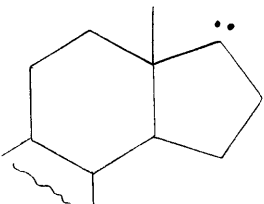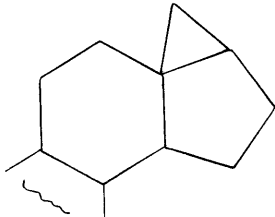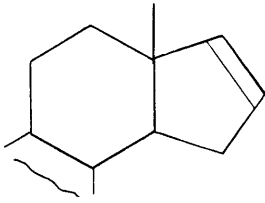
Pyrolysis of 78 with one equivalent of sodium methoxide in

refluxing diglyme (160°) gave a mixture of 13β,17β-methylene-

androst-5-ene-3β-ol 79 and 5,16-androstadiene-3β-ol 80. Optical

rotation indicated this crude mixture consisted of 68% 79 and 32%

80. Since components 79 and 80 could not be separated by regular

column chromatography, common techniques could not be employed

in the separation process. After recrystallization efforts proved

unsuccessful, a chromatographic method of separation was developed employing silica gel impregnated with silver nitrate. This separation process afforded 79% of the γ-insertion product 79 and 21% of product 80, in fair agreement with the rotation measurement. Structures 79 and 80 were easily assigned on the basis of spectral data presented in the Experimental Section.

The development of column chromatography on silica gel impregnated with silver nitrate (details given in the Experimental Section) was essential not only for this separation but for the success of this entire project. Although it has been known for some time that silver nitrate complexes with olefins, this property has not found extensive use in column chromatography, but it has found wide use in thin layer chromatography (T. L. C.). Silver nitrate impregnated silica gel has been used in petroleum chemistry for separating cis-trans isomers and for selective adsorption of olefins from hydrocarbons (101). This technique has also been used in some natural products work by Ourrison et al. (100). The column chromatography technique developed in this work proved to be more efficient than the methods used by these workers. The method is obviously preferable to laborious preparative thin layer chromatography.

The high ratio of γ/β insertion from 78 was surprising since in most cases "hydride shift" occurs more readily than γ-insertion (Table 16).

Table 16. Reactions of β-Methyl Cyclopentylidenes.

Carbene	γ-insertion	β-insertion
(9)	10%	55% 35%
(9)	25%	75%
	79%	21%

One possible explanation for the larger amount of cyclopropane formation in the steroid system is conformational in nature. Ring D is quite rigid in steroids whereas the free cyclopentanes are conformationally mobile. The latter, therefore, would appear better able to assume the necessary geometry for β-insertion (hydride shift). In the fixed steroid carbene, the C-16 hydrogens are bisectional in

nature and possibly less able to migrate.

It was felt that the increased amount of cyclopropane formation could also be due to generation of a poorly solvated carbonium ion from proton sources such as -OH and -NH functional groups, or even residual methanol. The formation of a cyclopropane ring from such a carbonium ion has good analogy in studies made on cyclopropyl tosylhydrazone 81 (12). Cyclobutene 82 was the major
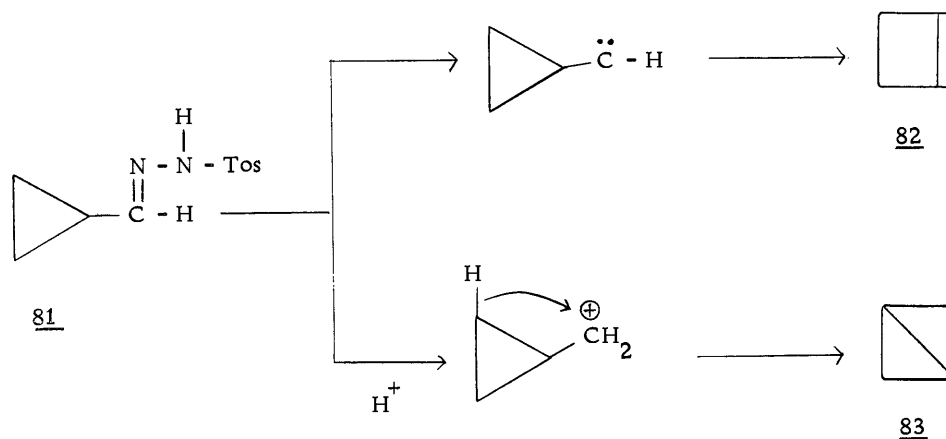
product in aprotic media (excess base), but was replaced by bicyclobutane 83 in protic media (excess tosylhydrazone). It was proposed that 82 was formed primarily by a carbenic process, while 83 was formed through a cationic process.

The possibility that cyclosteroid 79 arose from a carbonium ion was tested by decomposing tosylhydrazone 78 in the presence of varying amounts of sodium methoxide. The relative yields of γ-insertion and β-insertion products were determined from integration of olefinic bands of the NMR spectra of the mixtures. The effect

of changing base concentration in this reaction is shown in Table 17.

Table 17. Effect of Base on the 79:80 Ratio.

Equivalents of NaOMe	79/80	Other Products
0.5	ca. 2.0	ca. 54%
1.0	3.1	---
2.0	2.0	---
5.0	2.0	---

If an equilibrium between 84 and 85 is established, excess base will shift it to the left and the products under these conditions are more likely true carbene products. The slightly larger percentage of cyclopropane compound with lower amounts of base indicates some γ-insertion is probably also resulting from a carbonium ion intermediate derived from 85.
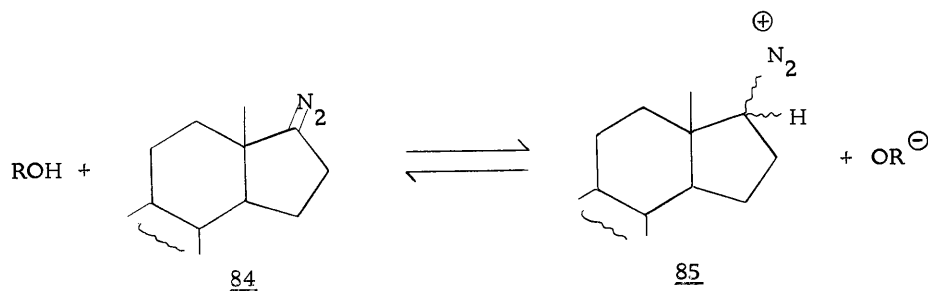
The sodium salt of 78 was also decomposed photolytically as a suspension in tetrahydrofuran. It was thought that perhaps a lower decomposition temperature might influence the ratio of 79 and 80, or

even provide a product not observed in the pyrolytic decomposition.

This reaction gave a mixture in which the major fraction consisted of

71% of cyclosteroid 79 and 29% of 5, 16-androstadiene-3β-ol 80.   The

ratio of γ/β insertion for the photolytic reaction is nearly the same as

the ratio from the pyrolytic reaction.

After this work Caglioti et al. (15) reported a similar synthesis

of a 13β,17β-methylene steroid.   Under the conditions of these

workers, tosylhydrazone 86 (the 5, 6-dihydro analog of 78), was

treated with a large excess of lithium hydride in boiling toluene to

give a mixture of cyclosteroid 87 and an unidentified olefin.   Product

87 was separated from the olefin by ozonolysis of the mixture

followed by column chromatography.   Cyclosteroid 87 was reported

to make up 67% of the mixture.   This reaction was repeated under
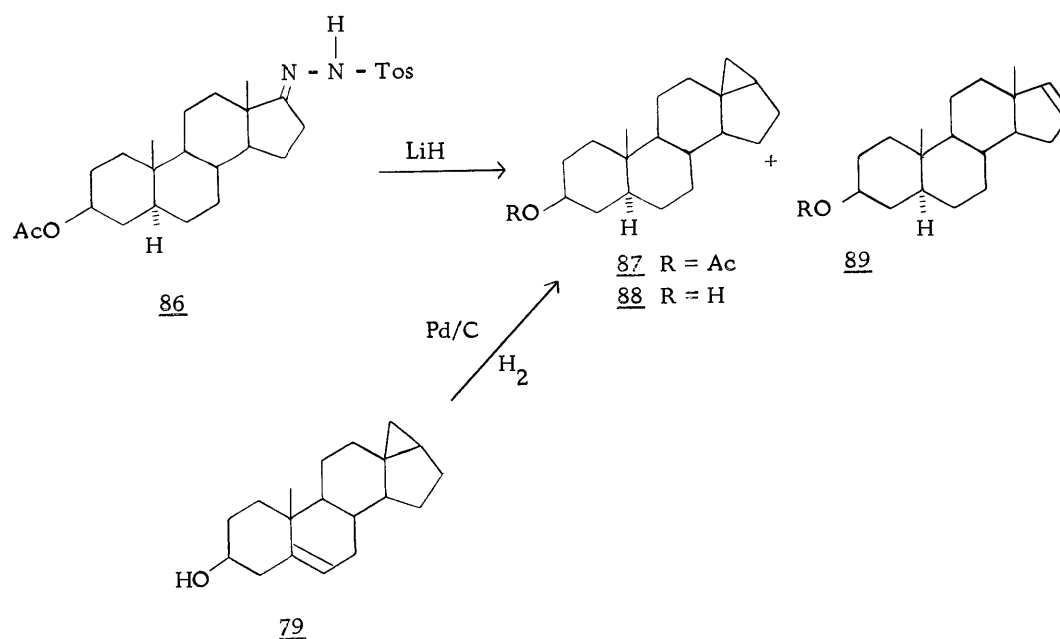
our conditions so a comparison of results could be made. When

tosylhydrazone 86 was treated with sodium methoxide and heated in

refluxing diglyme, a mixture of 88 and 89 was obtained. Column

chromatography on silver nitrate impregnated silica gel afforded

72% of 88 and 28% of 89. The two cyclosteroids, 79 and 88, were

then interrelated by hydrogenation of 79. Under our conditions the

amount of insertion was somewhat higher than that reported by

Caglioti et al. This difference may be due either to the less accurate

measurements of Caglioti et al., and/or the difference in the amounts

of base used. The studies made on the carbenic decomposition of

17-keto tosylhydrazones are summarized in Table 18.

Table 18. Decompositions of Tosylhydrazones 78 and 86.

Tosyl-hydrazone	Base	Method of Dec.		
78	NaOMe (5 eq.)	Δ	2.0	68%
78	NaOMe (1 eq.)	hν	2.4	80%
86	NaOMe (1 eq.)	Δ	2.5	61%
86 (15)	NaH (62 eq.)	Δ	2.0	86%

Cyclization onto C-19. The exciting finding that one could

achieve predominant carbene γ-insertion onto the C-18 methyl group

prompted an immediate study of a similar approach to the C-19

methyl. Similar cyclization from C-1 carbenes would lead to 1β, 19β-

cyclosteroids of potentially great interest both in themselves and as

further synthetic intermediates. At present, the only route to such

cyclosteroids requires previous activation at C-19 (130). The key

step of that route involves cyclization of hydroxyketone 91.
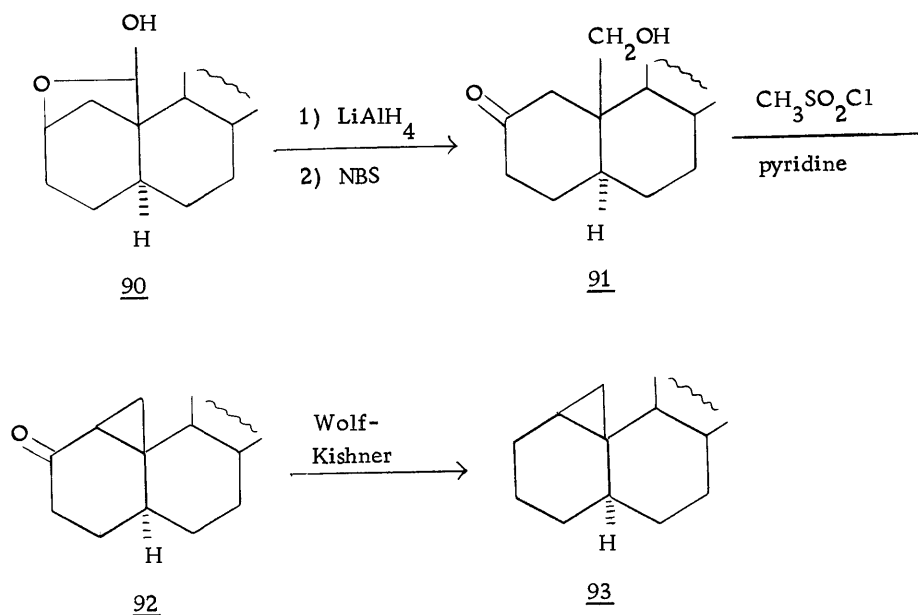
1-Ketocholestane tosylhydrazone I-103 was prepared by a

previously described route shown in Scheme 3. It should be noted

that all of the ketones formed in this route were precursors for

tosylhydrazones which were also studied in this work. Pyrolysis

of the sodium salt of I-103 afforded a mixture containing only 5% of

1β, 10β-methylene-cholestane 104 and 95% of 1-cholestene 105.

Chromatography of this mixture on silver nitrate impregnated silica

Scheme 3

$$\underline{94} \xrightarrow[\text{PtO}_2]{\text{H}_2} \underline{95} \xrightarrow[\text{H}^+]{\text{Na}_2\text{Cr}_2\text{O}_7} \underline{96} \xrightarrow[\text{HOAc}]{\text{Br}_2}$$

$$\underline{97} \xrightarrow[\text{CaCO}_3]{\text{DMF}} \underline{98} \xrightarrow[^-\text{OH}]{\text{H}_2\text{O}_2} \underline{99} \xrightarrow{\text{H}_2\text{N}-\text{NH}_2}$$

$$\underline{100} \xrightarrow{\begin{array}{c}\text{Jones}\\\text{Oxidation}\end{array}} \underline{101} \xrightarrow[\text{Pd/C}]{\text{H}_2} \underline{102} \xrightarrow{\text{Tos-N-NH}_2} \underline{103}$$
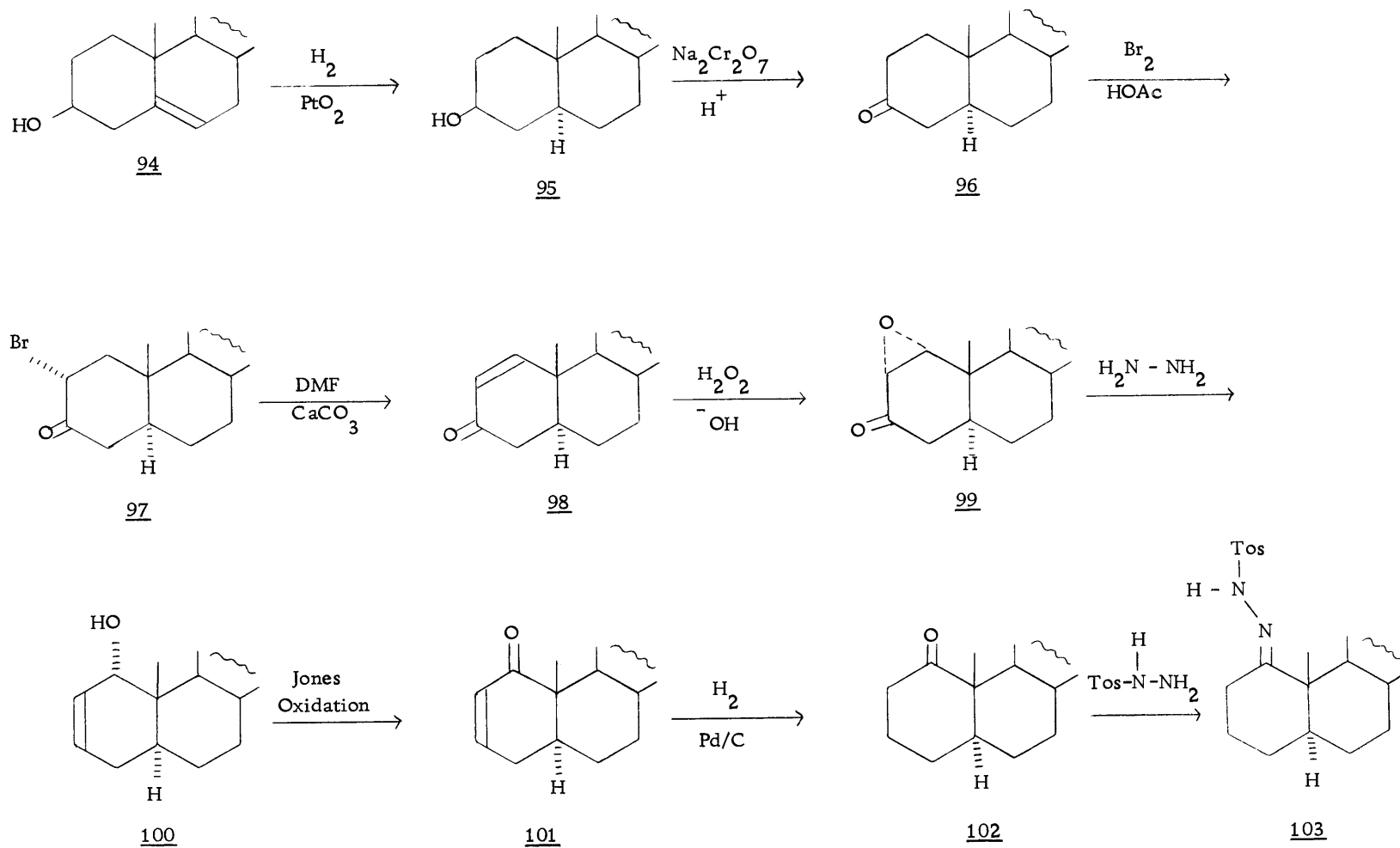
I - Cholestane series

II - Androstane series

57
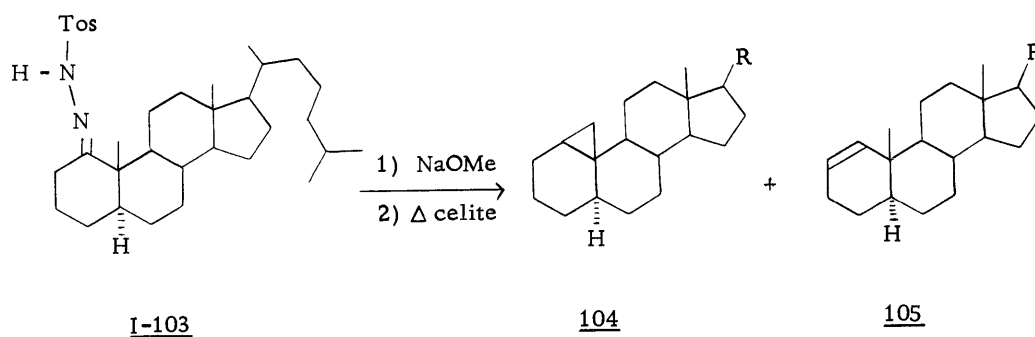
gel gave a 4% yield of 104 and an 80% yield of 105. Insertion product

104 was identified by its NMR and infrared spectra and a comparison

of its melting point with that reported in the literature.

The much larger amount of insertion from the 17-carbene

compared to the 1-carbene was quite surprising. One must assume

that either the cyclohexane ring has a worse geometry for cyclo-

propane formation or a better one for hydride shift. Examination

of models offers little in the way of clues and a more detailed study

will be necessary to fully evaluate these results.

α, β-Unsaturated Carbenes

The major portion of this thesis was concerned with reactions

of rigid α, β-unsaturated carbenes (β-alkenyl carbenes). The

unusual features to be expected for such systems were discussed in

the Introduction Section. The reactions studied involved formation

of the α,β-unsaturated tosylhydrazone, conversion to its sodium

salt, and themolysis to the carbene as illustrated for the 4-cholesten-

3-one tosylhydrazone 57 in Scheme 4. Tosylhydrazone 57 represented

our most widely studied system. We originally hoped that carbene

108 would offer a simple route to 2,4-diene 109. Since saturated

cyclic carbenes give olefins in high yield, such a sequence seemed

to be an excellent route to dienes. Such a reaction pathway has

actually been discovered leading to the relatively facile preparation

of 109, but of greater interest was the discovery of novel inter-

molecular reactions which decrease the yield of 109. Attack on

solvent has been observed with all solvents investigated, leading to

many interesting compounds and pointing up the large differences in

reactivity between saturated and conjugated carbenes.

In only one case were these solvent derived products observed

with the saturated systems. From a mechanistic point of view it is

most difficult, however, to determine which of the three possible

intermediates 106, 107, or 108 gives rise to intermolecular products.

When solvent derived products were observed by other workers, a

carbene was usually assumed to be the reactive intermediate (68, 95).

To illustrate these problems one can consider the cyclopropyl

adducts formed when the decomposition was carried out in an olefinic

solvent such as cyclohexene (Scheme 5). Whereas saturated carbenes

give no such adducts, unhindered unsaturated carbenes gave adducts

Scheme 4
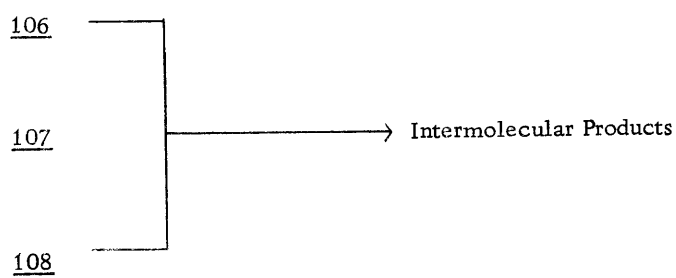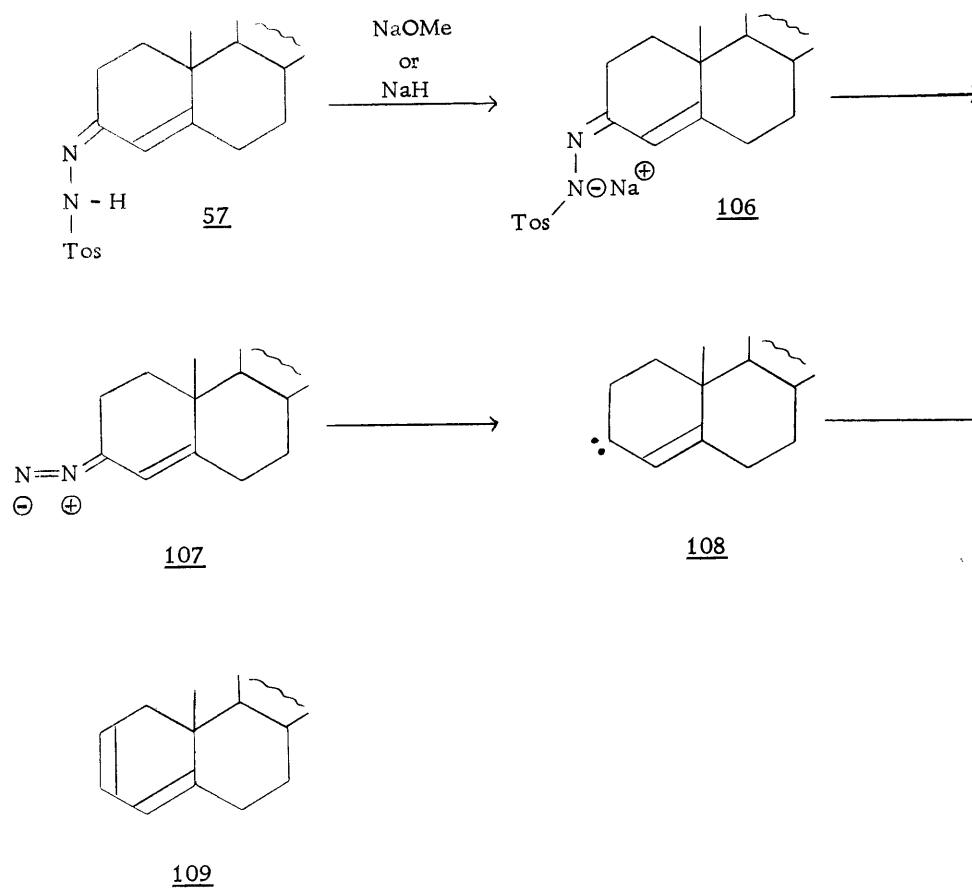
with cyclohexene. The problem is that although the carbene 108

seems a logical precursor, pyrazoline 110, formed as indicated,

cannot be ruled out as a reactive intermediate in the formation of 111.

Decomposition of 4-Cholestenone Tosylhydrazone 57 in Toluene.

The first α,β-unsaturated tosylhydrazone to be investigated was 4-

cholestenone tosylhydrazone 57. The initial reaction conditions

employed sodium methoxide in toluene as solvent. Toluene was

chosen as solvent since Caglioti et al. had used this medium success-

fully in their pyrolysis of 7-keto-cholesterol-acetate tosylhydrazone

54. Under these conditions, tosylhydrazone 57 was expected to give

a good yield of 2,4-cholestadiene 109. Normal work-up procedures
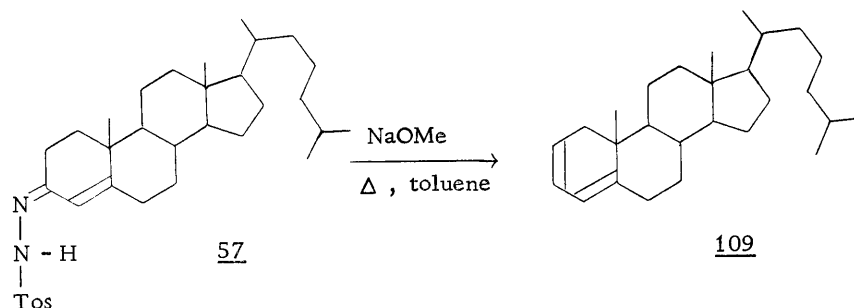
followed by alumina chromatography gave, however, only low yields

of 109, and as many as seven additional products. From thin layer

chromatography and spectral studies made after alumina chromatog-

raphy, it was possible to establish the presence of 3,5-cholestadiene

112, 4-cholesten-3α-ol 113, 4-cholesten-3β-ol 114 and what appeared

to be products arising from carbene insertion into the carbon-

hydrogen bonds of toluene 115.

Scheme 5

112   113   114   115
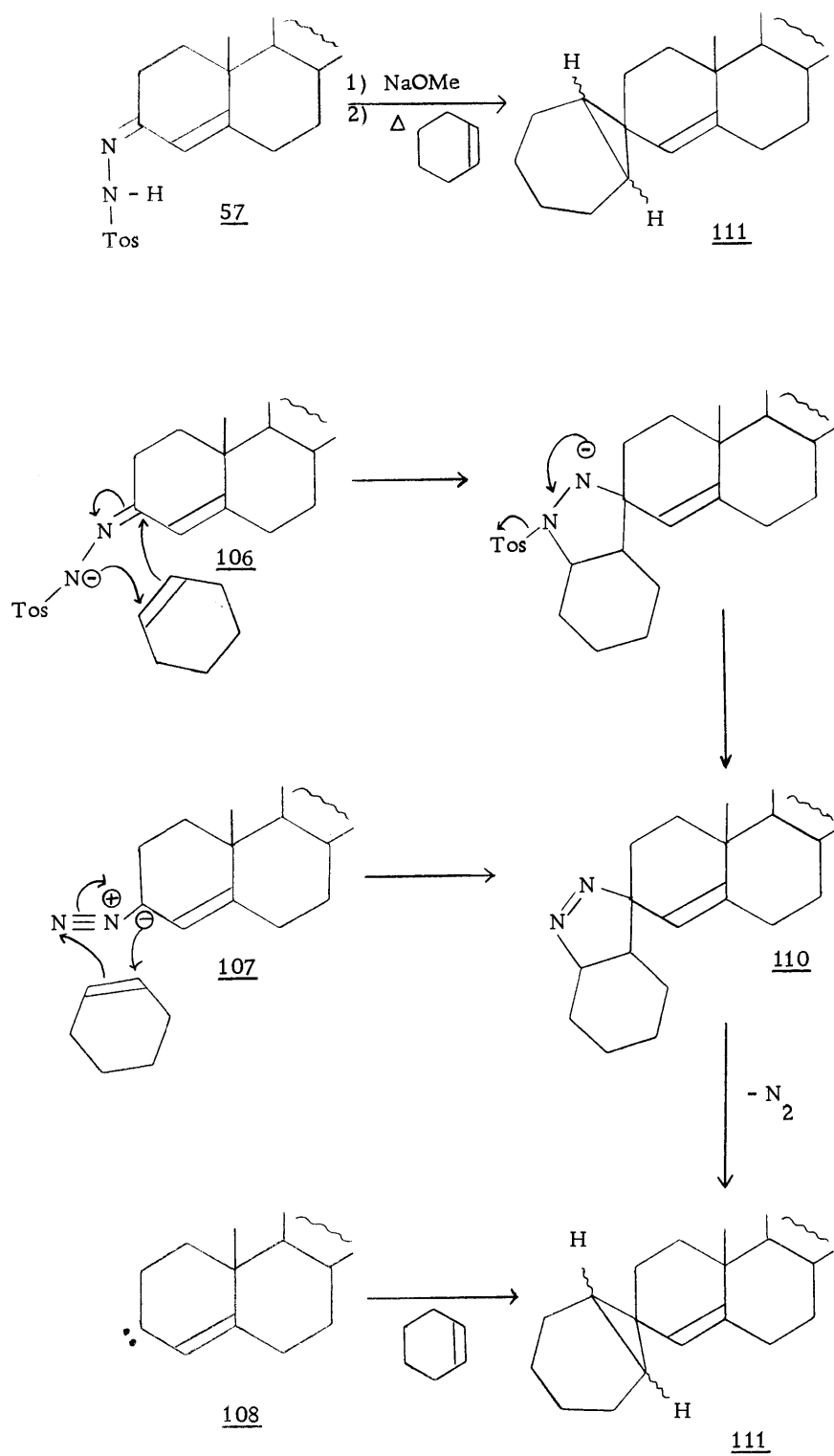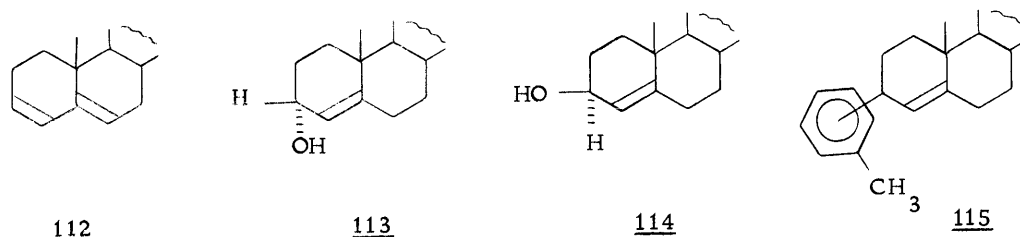
No quantitative measurements of these components could be made.

Because the hexane (non-polar) fractions from column chromatography

gave mixtures of inseparable compounds containing an aromatic ring,

it was decided to change the solvent to benzene. If, indeed, attack

on the solvent were occurring, the use of benzene as solvent should

reduce the number of non-polar products.

Decomposition of 4-Cholestenone Tosylhydrazone 57 in

Benzene. A careful thin layer chromatography study of the initial

product mixtures from the decompositions of tosylhydrazone 57 in

benzene showed that the least number of products was obtained when

excess sodium methoxide was utilized. From reactions employing

2 equivalents of base, only two major polar components were

observed. It was also found that the two polar components disappeared

on alumina chromatography and gave rise to three new products.

When the two original polar components were allowed to stand on

silica gel, no reaction occurred. Once the best reaction conditions

(excess base) and a suitable adsorbent (silica gel) had been found,

a product study was possible. Under the prescribed conditions,

2,4-cholestadiene 109 and spiroheptatriene 116 were the non-polar

components and the 3α- and 3β-methyl ethers, 117 and 118, were the

major polar components.

109   116

1) NaOMe

2) Δ,

H   CH₃O

OCH₃   H

117   118
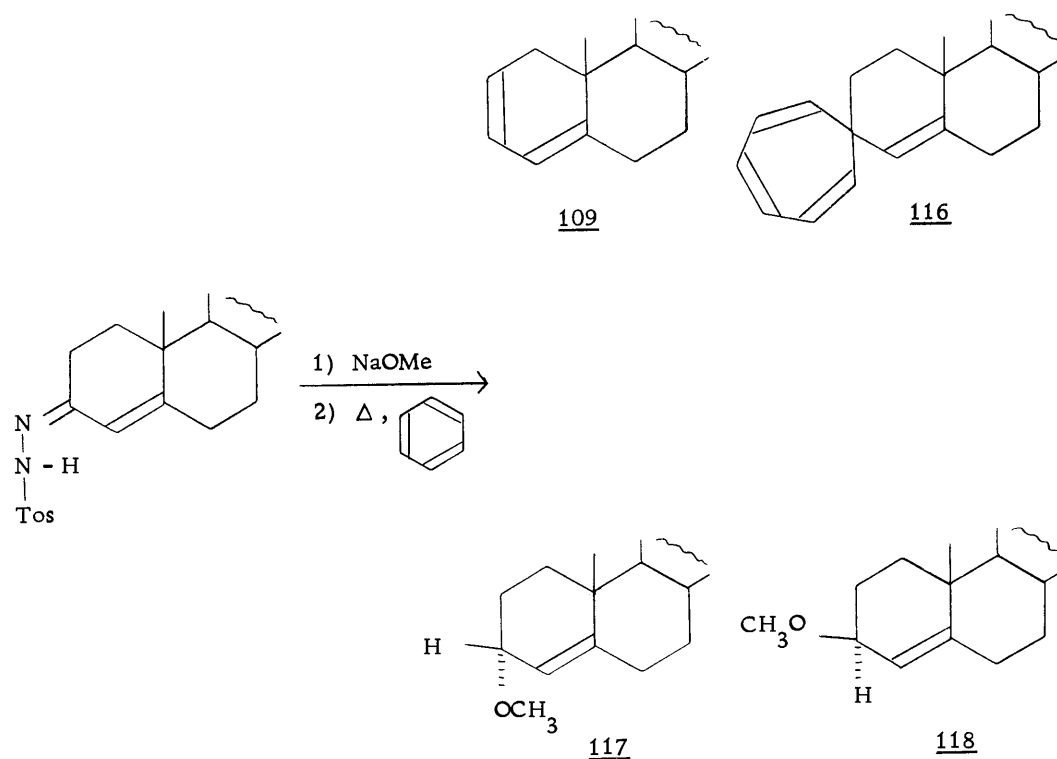
Diene 109, 42% of the product mixture, was identified by

agreement of its physical properties with those reported in the

literature and particularly by its ultraviolet and NMR spectra.

The ultraviolet spectrum shows a maximum at $266m\mu$, $\epsilon = 5100$ and

the NMR spectrum exhibits an olefinic pattern at 5.58δ (Fig. 1)

identical to that reported for other 2,4-dienes (6).

Figure 1.   Olefin Band of the NMR Spectrum of 109.
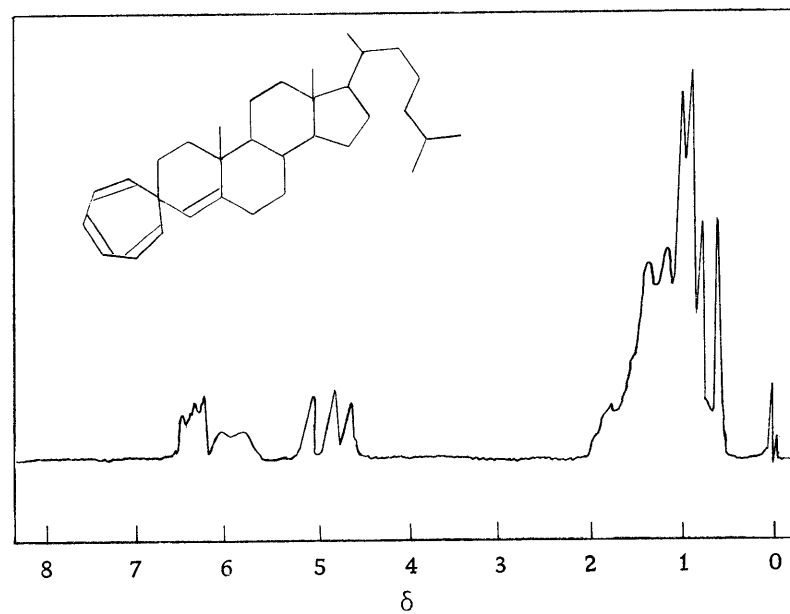
Figure 2.   The NMR Spectrum of 116.

Identification of tropilidene $\underline{116}$ (42% of the product mixture)
was based on a satisfactory analysis and its ultraviolet and NMR
spectra. The NMR spectrum (Fig. 2) shows seven olefinic hydrogens,
with one at 5.12 δ assigned to a C-4 olefinic hydrogen due to the
typical location (1 p.p.m.) of the C-19 methyl group. In addition,
there were two proton bands at 6.37 δ and 6.05 δ, and a single proton
doublet at 4.85 δ, all attributed to the tropilidene ring. The NMR
bands attributed to the tropilidene ring of $\underline{116}$ are in good agreement
with those reported for 7,7-dialkyltropilidene $\underline{35}$ (95).

	1,6-H	2,5-H	3,4-H
$\underline{35}$	4.61 δ	6.30 δ	6.58 δ
$\underline{103}$	4.85 δ	6.05 δ	6.37 δ

Compound $\underline{118}$ made up 2% of the product mixture and its assign-
ment as a β-methyl ether was based upon agreement of its melting
point with that reported for the known compound, and on its spectral
data. Identification of the 3α-methyl ether $\underline{117}$, which composed 9%
of the reaction mixture, was based largely upon its elemental

analysis and its NMR spectrum.

The two non-polar products probably arise from a carbene inter-
mediate, the diene 109 from the expected "hydride shift", and the
steroidal tropilidene 116 from the completely unexpected addition of
the carbene to benzene, followed by ring opening of the intermediate
norcaradiene 119. The formation of 116 from a transient pyrazoline
cannot be ruled out. Insertion of the carbene into the "O-H" bond of
trace amounts of methanol provides an attractive route to the methyl
ethers. Deliberate addition of methanol to the reaction mixture
resulted in the formation of only 117 and 118 in a ratio of approxi-
mately 3:1 indicating that the carbene is selectively attacked from
the α-side.
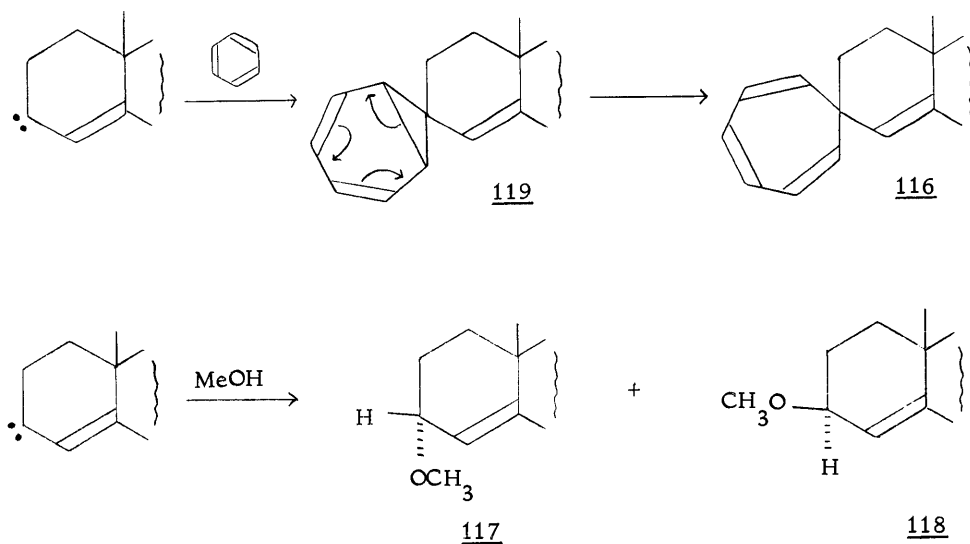
The formation of __116__ represents the first case, other than

cyclopropylidienes, in which intermolecular addition occurs when

β-hydrogen shift is possible. Of the many carbenes known to add to

benzene (shown in Table 19) none have β-hydrogens.

Table 19. Carbene Intermediates That Add to
Aromatic Compounds.

NC
    C:
NC
	F$_3$C
	    C:
	NC
		F$_3$C
		    C:
		F$_3$C
			φ
			    C:
			H

(2)	(2)	(56)	(81)

H
    C:
H
	H
	    C:
	ROOC
		N—φ ring
		—C – H
			Cl
			    C:
			Cl

(40)	(2)	(121)	(2)

Once the products from the pyrolysis of __57__ had been isolated

and identified, it was possible to locate the difficulties originally

encountered when alumina was employed as the separation medium.

Addition of either the α-methyl ether __117__ or the β-methyl ether __118__

to a column of neutral alumina (activity II) afforded approximately a

75% yield of 3,5-cholestadiene __112__ and a 15% yield of a mixture of

the 3α- and 3β-alcohols, __113__ and __114__. The isomeric alcohols were not
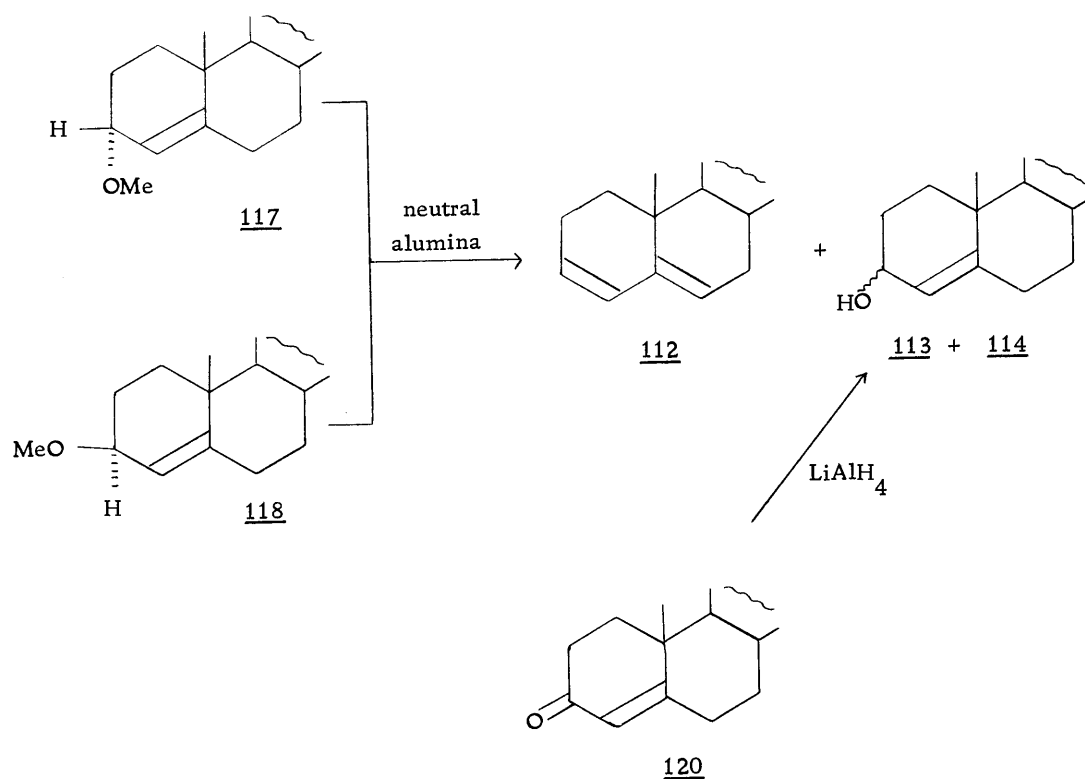
separated and their identification was accomplished by comparing the

infrared spectrum and TLC of this mixture to that of a mixture of the

alcohols synthesized by lithium aluminum hydride reduction of 4-

cholestenone 120.

Previous alumina chromatographies of the product mixtures

from pyrolysis of 57 gave compounds which contained an aromatic

ring. With this in mind, the conversion of 116 to 3-phenylcholest-

2-ene 122 was carried out on basic alumina. For comparison, 3-

phenylcholest-2-ene 124 was synthesized by an alternate route. The

infrared spectra of 122 and 124 are identical in all respects.

Comparisons of the spectral and physical properties of 122 and 124

are shown in Table 20. The mechanism of this alumina catalyzed

reaction will be considered later.
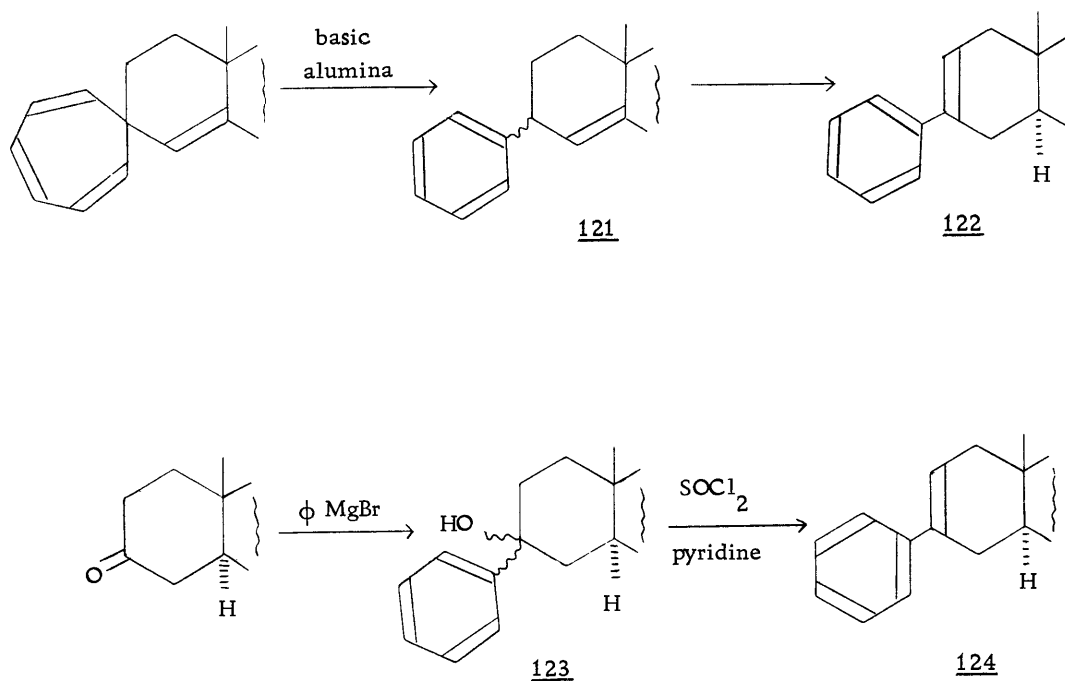
After the products of this reaction had been identified it was pos-

sible to turn attention to optimizing the yield of "carbenic products"

by studying the effects of changing base and sodium salt concentra-

tions. The optimum conditions found for this reaction could then be

applied to other α,β-unsaturated carbene reactions. The pyrolysis

of 57 with varying amounts of sodium methoxide in a constant

quantity of benzene showed that the type and ratio of products were

very dependent on the amount of base used (Table 21).

Table 20. Properties of 122 and 124.

compd.	I. R.	U. V.	Olefinic Bands	C-19	m. p.	$a]_D$
124	3020 cm^{-1} 748 cm^{-1} 690 cm^{-1}	248 mμ $\epsilon = 13,300$	6.0 δ	48.0 c. p. s.	137-138°	+65°
122	3020 cm^{-1} 748 cm^{-1} 690 cm^{-1}	248 mμ $\epsilon = 13,600$	6.0 δ	48.0 c. p. s.	133-136°	+58°

Table 21. NaOMe Treatment of 57.

Equivalents of NaOMe	Weight % of Non-Polars	109/116	Weight % of Polars	117/118
10	60%	0.9	40%	4.0
5	71%	1.1	29%	---
2	84%	1.0	16%	3.9
1	87%	1.0	13%	---
0.75	45%	1.1	*55%	none
0.50	37%	1.1	*63%	none

*corrected for excess tosylhydrazone

Conditions employing less than 1 equivalent of sodium

methoxide gave substantially lower yields of hydrocarbon products

than those employing 1 equivalent or more of base. In the runs

utilizing excess tosylhydrazone, the non-polar fraction consisted

mainly of a high melting dimer (m.p. 280-300°) whose ultraviolet

spectrum shows maxima at 308 mμ, ϵ = 10,600, 295 mμ, ϵ = 15,500

and 284 mμ, ϵ = 12,400. This material was not studied in detail

but a structure such as 127 seems reasonable. The polar components
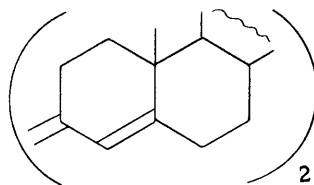
127

from reactions with excess tosylhydrazone contained no methyl ethers

and were complex mixtures. Although no attempt was made to

characterize these components, it is quite possible that they are

sulfinates 46 and N-tosylates 47 of origin described in the Introduction

Section.

As expected, reactions employing 1 equivalent or more of

sodium methoxide gave 109, 116, 117 and 118 as major products.

Unexpected, however, was the decrease in yield of non-polars, 109

and 116, with increasing amounts of sodium methoxide, though their

ratio remained constant. Since the amount of methyl ethers increases,

possibly the carbene is trapped by methoxide ion (with protonation

on work-up) or incompletely removed methanol.

It was also discovered that the yield of non-polar products 109

and 116 increased as the reaction was run under more dilute condi-

tions. These results, shown in Table 22, reflect the obvious

preference for increased hydrocarbon products under low concentra-

tion.

Table 22. Effect of Changing Sodium Salt 106
Concentration.

Molarity of Tosylhydrazone 57	Wt. of of Non-Polars	Wt. of of Polars
0.144	50%	50%
0.072	78%	22%
0.036	84%	16%
0.007	89%	11%

In summary, optimum yields of hydrocarbons 109 and 116

require 1-2 equivalents of sodium methoxide and pyrolysis in dilute

solutions.

Previous use of sodium hydride in tosylhydrazone decomposi-

tions seemed ambiquous and it was felt that the benzene--4-

cholestenonone tosylhydrazone system provided a good opportunity

to compare the role of this base to that of sodium methoxide. On

the basis of published data, sodium hydride might be expected to

react with 57 at C-2 or C-6 thus giving dienes directly (74), or it

might react with the "N-H" bond of the tosylhydrazone (113) to give

"carbenic products" 109 and 116. Pyrolysis of 57 with a huge excess
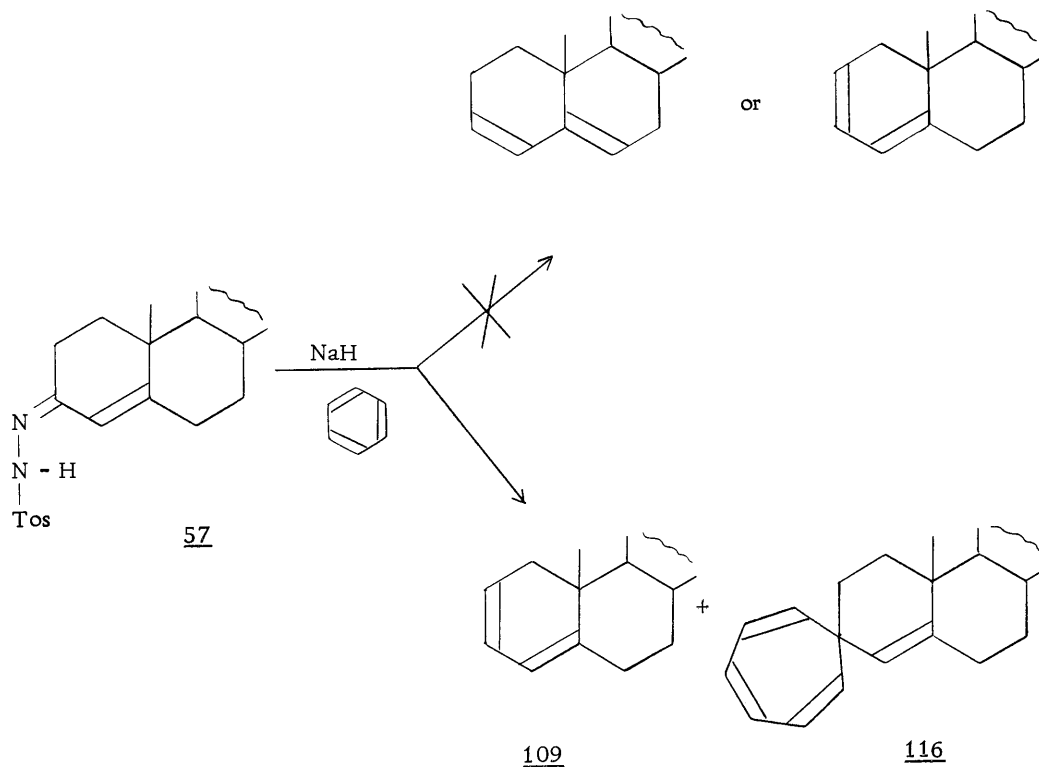
of sodium hydride in benzene gave 109 and 116 as the only non-polar

products. The yields of non-polar products were quite insensitive

to the amount of sodium hydride used (Table 23). The polar fraction

from sodium hydride decompositions was a complex mixture, the

chief component being starting tosylhydrazone in spite of the use of

excess base. The problem of polar components is probably due to

insufficient conversion of 57 to its sodium salt at the low reaction

temperature. Use of toluene (b.p. 110°) gave non-polar products in

yields of 80% or better with no starting tosylhydrazone remaining.

Table 23. NaH Treatment of 57.

Equivalents of NaH	Weight% of 109 + 116	109/116	Weight % of Polars
10	53%	1.0	47%
5	54%	1.1	46%
2	52%	1.0	48%
1	37%	1.0	63%

Decomposition of 4-Cholestenone Tosylhydrazone 57 in Diglyme

and in Heptane. Most tosylhydrazone decompositions have been

carried out in high boiling ether solvents such as diglyme, in which

very few unusual intermolecular reactions would be expected. Since

intermolecular attack of a dialkyl carbene on diglyme had not been

reported, it seemed this solvent might give the desired high yield of

2,4-cholestadiene 109. Pyrolysis of the salt of 57 did not, in fact,

give a high yield of diene. Chromatography of the reaction mixture

showed it to contain 35% of diene 109, 40% of inseparable products

resulting from insertion of the carbene intermediate into the various

bonds of diglyme 124, 10% of the α-methyl ether 117, 6% of the

β-methyl ether 118 and 8% of the α-sulfone 125.
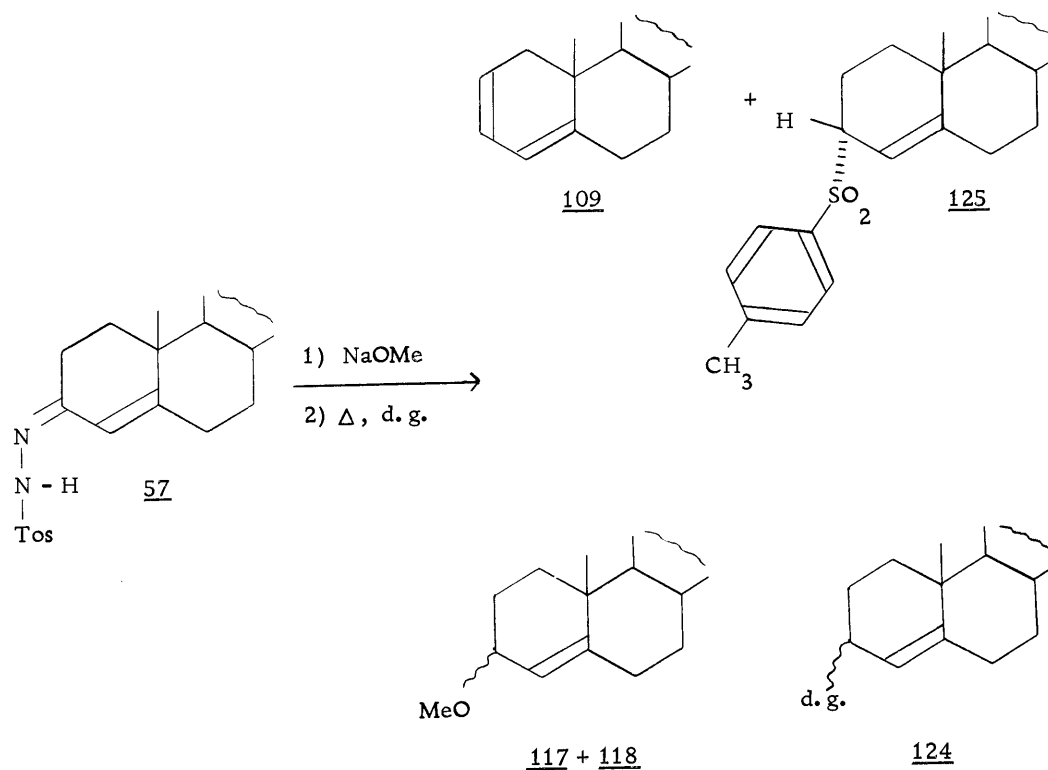
That **124** was derived from diglyme insertion was obvious from the NMR spectra of the mixture.

Since it was felt that C-H insertion α to an oxygen would be relatively favored, the tosylhydrazone was decomposed in a hydrocarbon solvent, n-heptane. Again, however, the product mixture was complex; 2,4-diene **109** (36%), an NMR identified mixture of insertion products **126** (51%), and a mixture (10%) of methyl ethers, **117** and **118**, and sulfone **125**. The formation of insertion products
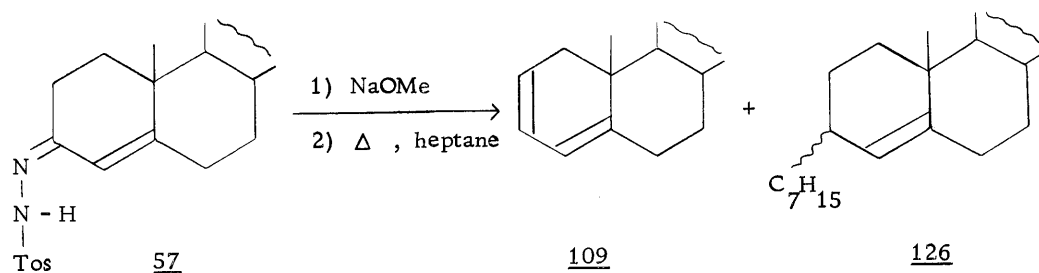
and sulfone 125 are indicative of a highly stabilized carbene inter-

mediate. It has already been pointed out that such products are

observed only when the dialkylcarbene is excessively stabilized.

Decomposition of 4-Cholestenone Tosylhydrazone 57 in Celite

and in Carbon Tetrachloride. Because carbene 108 added to aromatic

solvents and inserted into the "C-H" bonds of ether or hydrocarbon

solvents, it seemed reasonable that generation of 108 in the absence

of solvent might give a good yield of diene 109. Pyrolysis of the

sodium salt of 57 (from sodium methoxide) gave 2,4-diene 109 (30%),

a dimer which is thought to be 127 (12%) and a mixture (66%) of

methyl ethers 117 and 118 and sulfone 125. The high melting dimer,
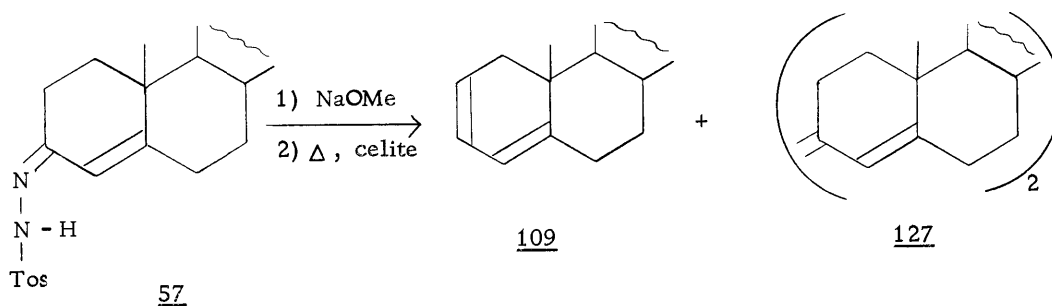
127, is also formed in reactions with high concentrations of sodium

salt (celite) or in cases where excess tosylhydrazone was used

(benzene). The dimer could arise from intermolecular trapping of

the carbene by diazo compounds, or as shown below, by sodium salt

106.
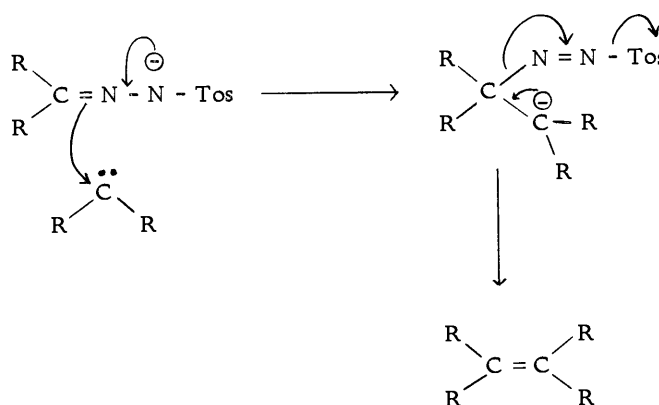
Obviously, dry decompositions eliminate intermolecular reactions

with solvent, but increase those with reactant.

Carbon tetrachloride was chosen as a final solvent in the

carbenic decomposition of 57 since most carbenes are inert to

"C-Cl" bonds and dimer formation could be avoided by running the

reaction at high dilution. Decomposition of the sodium salt 106

(from either NaOMe or NaH) in carbon tetrachloride gave a red tar

from which the major product could be isolated in 28% yield and

identified as 129. It is interesting to note that the rest of the mixture

Scheme 6
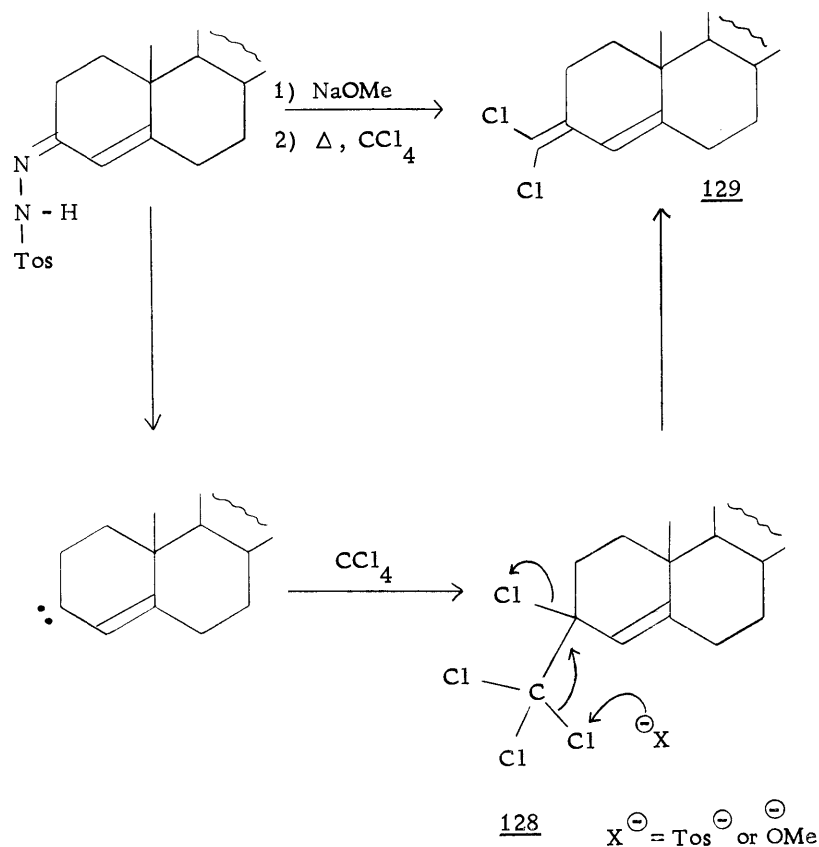
was very complex but did not contain the methyl ethers, 117 and 118,

or the sulfone 125. Identification of 129 was based upon a correct

elemental analysis and its spectral properties. The NMR spectrum

shows a broadened singlet at 6.07δ assigned to the C-4 proton. The

ultraviolet spectrum gives a maximum at 260 mμ, ε = 21,000.

Although the route to 129 is not clear, a possible pathway might

involve formation of insertion product 128 followed by an E-2

elimination with a base. The source of such a base is questionable,

but it is conceivable that the formed sodium p-toluenesulfinate or

the excess sodium methoxide might be able to cause this elimination

(Scheme 6). Such a mechanism would be analogous to that of E-2

eliminations of vicinyl dibromides with sodium iodide (127). The

pyrolysis of 57 in carbon tetrachloride is especially fascinating since

only two examples of trapping by "C-Cl" bonds have been reported

(eg. 130 and 131) (87, 121). This particular reaction deserves further

study in view of the potential utility of such compounds both as drugs

and further synthetic intermediates.

130

131
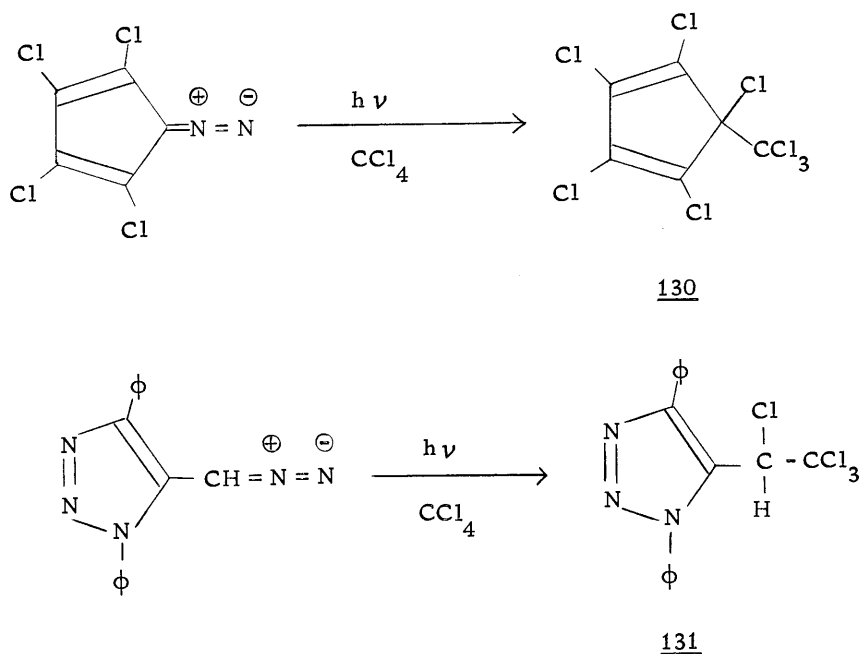
Decomposition of 4-Cholestenone Tosylhydrazone 57 in Cyclo-

hexene and in Tetrachloroethylene. Pyrolysis of 57 in the previous

cases provided unusual and unexpected products and it was of interest

to investigate further the properties of the carbene intermediate 108.

Still to be decided was whether this intermediate was exhibiting

nucleophilic or electrophilic properties. For this reason 57 was

pyrolyzed in the nucleophilic olefin cyclohexene, and then in the

electrophilic olefin tetrachloroethylene. The mixture of components

from the reaction in cyclohexene consisted of adducts 132 and 133

(23% and 24%) and insertion products 134 and 135 (14% and 9%). The

polar components consisted of α-methyl ether 117 (3%), β-methyl

ether 118 (2%) and α-sulfone 125 (14%). The assignment of

132   133

134   135
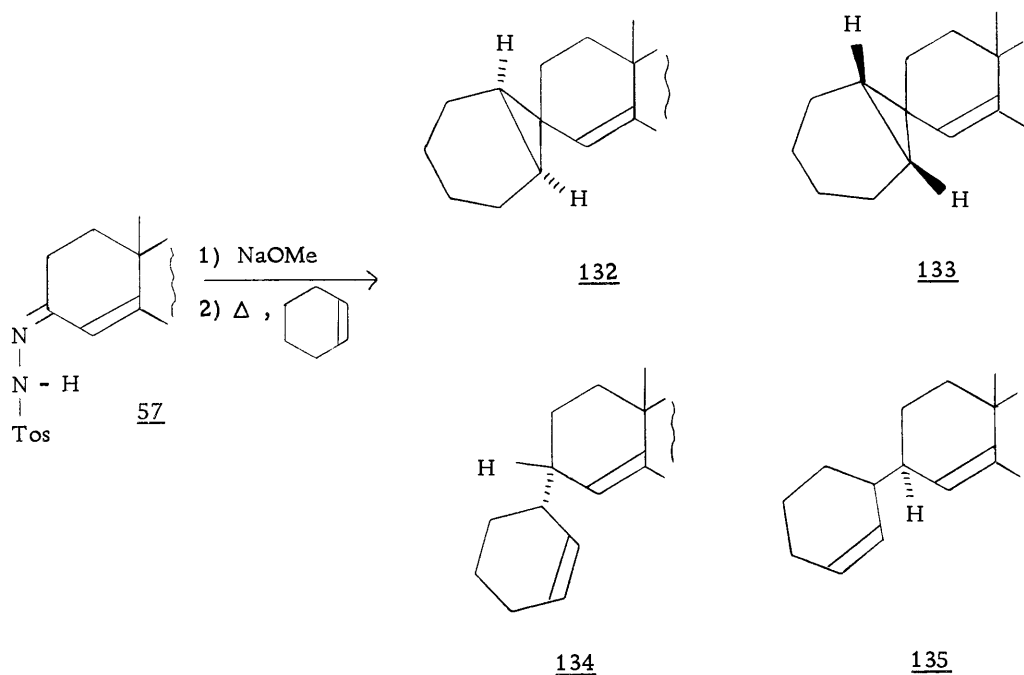
stereochemistry to isomers <u>132</u> and <u>133</u> was based largely upon the

order of elution from silver nitrate impregnated silica gel. From

examination of models, the double bond of <u>132</u> seems quite

inaccessible and <u>132</u> should therefore be eluted before <u>133</u>. The

NMR spectrum of adduct <u>132</u> shows a broadened singlet at 5.0 δ and no

other bands outside the methylene envelope. Its ultraviolet spectrum

shows a maximum at 211 mμ, ϵ = 14,600. The NMR spectrum of the

other isomer, <u>133</u>, is nearly identical to that of <u>132</u> except that the

C-4 olefinic proton is shifted upfield to 4.37 δ. A likely explanation

for this shift is that the C-4 proton of <u>133</u> is in the shielding cone of

the cyclopropane ring while the corresponding proton of <u>132</u> is not.

The ultraviolet spectrum of product <u>133</u> shows no maximum above

207 mμ.

Since pyrolysis of <u>57</u> gave cyclopropyl derivatives from cyclo-

hexene, it was expected that decomposition in the electrophilic olefin

tetrachloroethylene would favor diene formation. Surprisingly, the

tetrachlorospiro steroid <u>136</u> was formed in good yield (75%). The

polar fraction (25%) contained <u>117</u>, <u>118</u> and <u>125</u>. Use of sodium
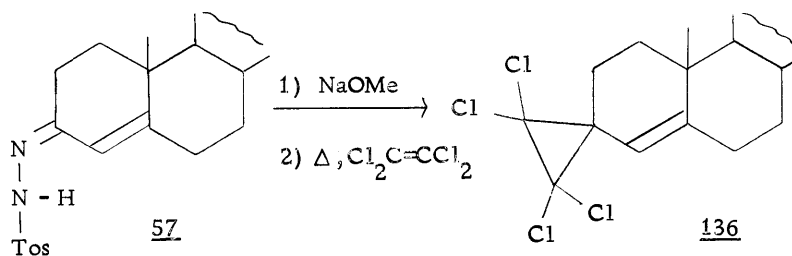
hydride as the base again gave <u>136</u> as the major product. Product

<u>136</u> gave a correct elemental analysis and an NMR spectrum which

shows one sharp band at 5.12δ and no other absorption outside of the

methylene envelope. Its ultraviolet spectrum shows a maximum at

206 mμ, ε = 14, 100. Thus, addition occurs to both nucleophilic

and electrophilic olefins.

A competition study was run using an equimolar mixture of the

two olefins in the hope that an early intermediate might be trapped by

the electron deficient olefin. The results were surprising as <u>132</u>,

<u>133</u>, <u>134</u>, <u>135</u> and <u>136</u> were all formed. The ratio of <u>136</u> to cyclo-

hexene derived products (<u>132</u> - <u>135</u>) was shown to be 1:2 by integration

of the representative bands in the NMR spectrum of the mixture.
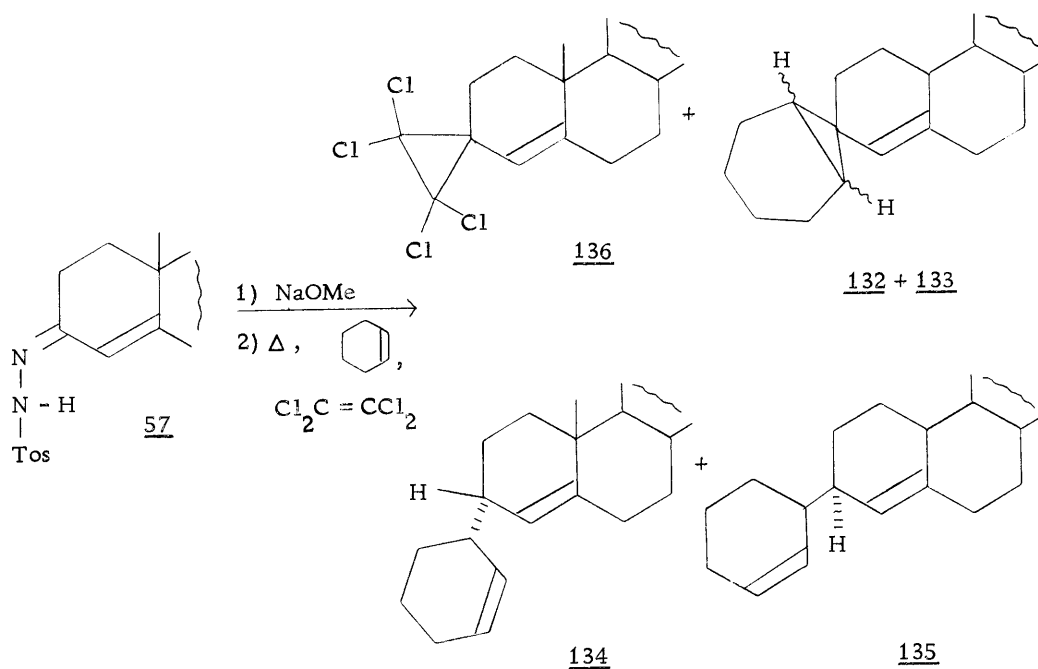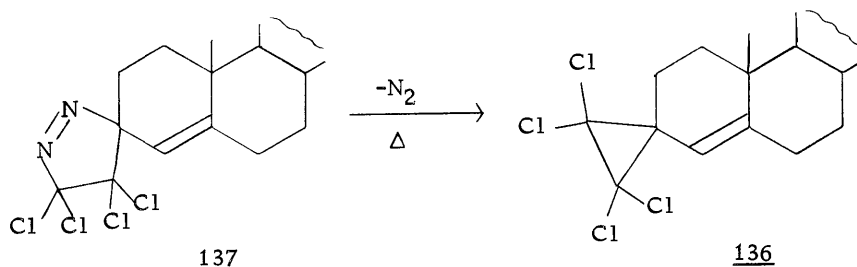
There is little doubt that the adducts are spirocyclopropyl steroids but this cannot be considered as proof that carbene 108 is the reactive intermediate. It is conceivable that spiro adducts, especially 136, may be preceded by a pyrazoline, 137 or 110, which could be formed from reaction of the olefin with the sodium salt 106 or with the intermediate diazo compound 107 (see Scheme 5). In this case, the formation of insertion products, 134 and 135, speaks either for a carbene intermediate which adds to both types of olefins, or for competitive formation of carbene 108 and pyrazoline 137. If electron donation of the β-double bond of carbene intermediate 108 is sufficient, it is possible 108 might react with both nucleophilic and electrophilic olefins. On the other hand, if pyrazoline formation is occurring, it is probable that this comes about from the sodium salt 106 rather than from an intermediate diazo compound. Unfortunately, no studies have been made on the reaction of tosylhydrazone sodium salts with electrophilic olefins, but Huisgen (65) and others (23) have studied 1,3-dipolar additions of unsaturated diazo compounds.

Such diazo compounds, due to the dispersion of negative charge of
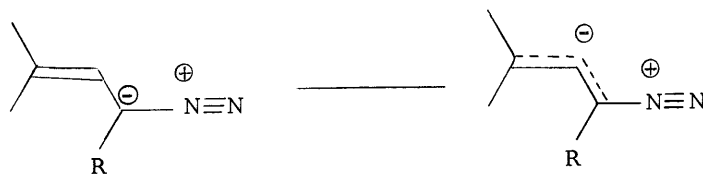
the cannonical form shown above, are generally unreactive in 1,3-dipolar additions. Also, non-conjugated double bonds reportedly show low reactivity to 1,3-dipolar additions (65).

The results of the decompositions of 57 in various media are summarized in Table 24.

Decomposition of Cholestanone Tosylhydrazone 138 in p-Xylene and in Tetrachloroethylene. Though the decomposition of 57 in various solvents gave numerous but interesting products, the question remained whether their formation was confined to α,β-unsaturated intermediates or whether the saturated analogs could react in a similar manner. It was therefore of interest to decompose cholestanone tosylhydrazone 138 in an aromatic solvent even though Caglioti (15) had also studied this reaction with lithium hydride in toluene solvent. Since saturated tosylhydrazones generally require

Table 24. Products From the Pyrolysis of 57 in Various Media.

Medium	Wt. % of Diene 109	Wt. % of Add'n Prod.	Wt. % of Insert'n Prod.	Wt. % of Dimer	Total Non-Polars	Wt. % of 117	Wt. % of 118	Wt. % of 125	Total Polars
Celite	30%	---	---	12%	44%	***	***	***	66%
Diglyme	35%	---	40%	---	35%	10%	6%	8%	65%
Heptane	36%	---	51%	---	90%	***	***	***	10%
Benzene	42%	42%	---	---	84%	9%	2%	---	16%
Cyclohexene	---	47%	23%	---	79%	3%	2%	14%	21%
Tetrachloro-ethylene	---	75%	---	---	75%	***	***	***	25%
Carbon Tetrachloride	---	---	28%	---	41%	---	---	---	59%

*** - present via T.L.C. detection

conditions - 2 equivalents of NaOMe; sodium salt conc. = 0.036 M.

1) NaOMe

2) Δ,

N
||
N-H   H
|
Tos   138

139

140

48

H
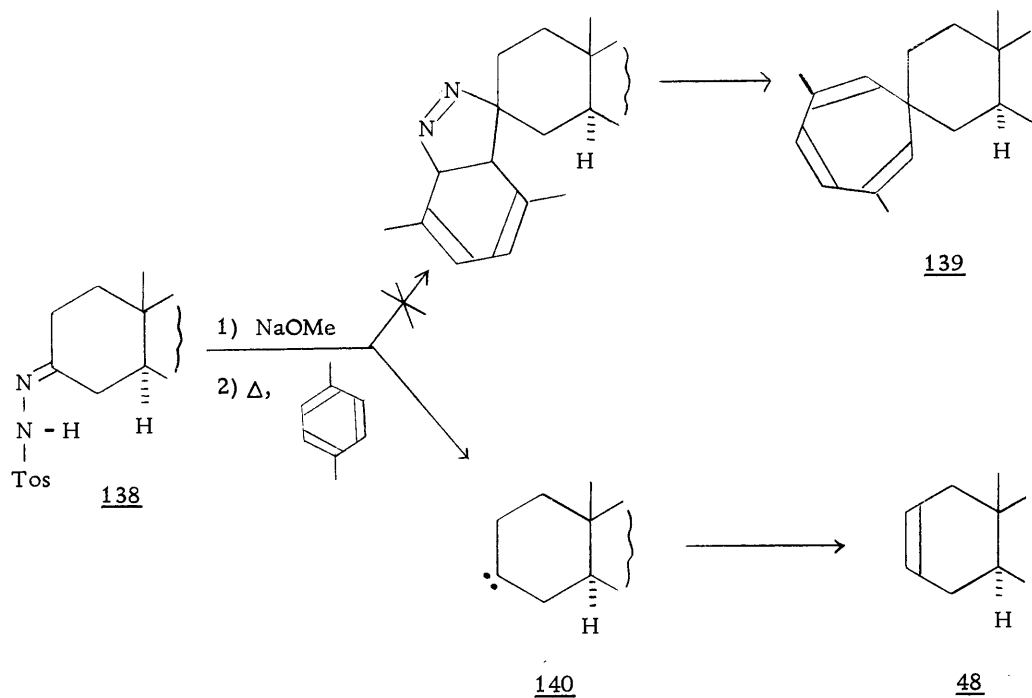
much higher decomposition temperatures than do α, β-unsaturated

tosylhydrazones, p-xylene (b. p. 150°) was chosen. In accord with

Caglioti's results, this reaction afforded 2-cholestene __48__ in 90%

yield. The infrared spectrum of product __48__ is identical to that of an

authentic sample of 2-cholestene and quite different from that of an

authentic sample of 3-cholestene. No trace of products resulting

from reaction with solvent were found and no methyl ethers were

formed. Since no spirotropilidene __139__ was formed with the saturated

carbene, such addition with __108__ is a result of the conjugated double

bond. The stability offered might allow the carbene __108__ to select

between intramolecular insertion and addition, although one cannot

rule out a conformation change as the source of the decreased β-

insertion.

Saturated tosylhydrazone 138 was also pyrolyzed in tetra-

chloroethylene. Work-up procedures involving column chromatog-

raphy on neutral alumina gave 2-cholestene 48 in 60% yield. When

the chromatography separation was carried out on silica gel,

pyrazoline 141 was isolated as the major product (58%) along with

the trichloroethylene isomers 142 (24%) and 2-cholestene 48 (10%).
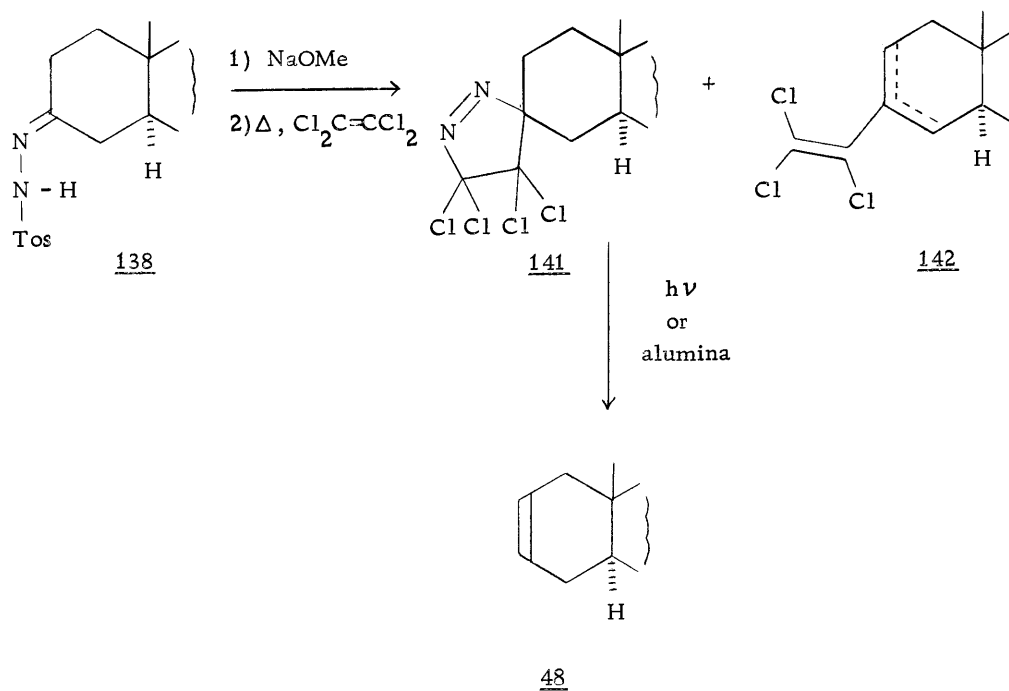
The minor products, 48 and 142, probably arise from the major

product 141. Pyrazoline 141 was photolyzed in the hope of obtaining

a tetrachlorocyclopropyl steroid, but only 2-cholestene was obtained.

The major product of the pyrolysis reaction, 141, may be formed by

addition of either sodium salt or intermediate diazo compound to the

solvent. Its formation does not necessitate that the tetrachloro-

cyclopropyl steroid 136 be preceded by a similar pyrazoline inter-

mediate 137. It does, however, demonstrate that pyrazoline 137

may possibly be formed. Pyrazoline 137 might be expected to lose
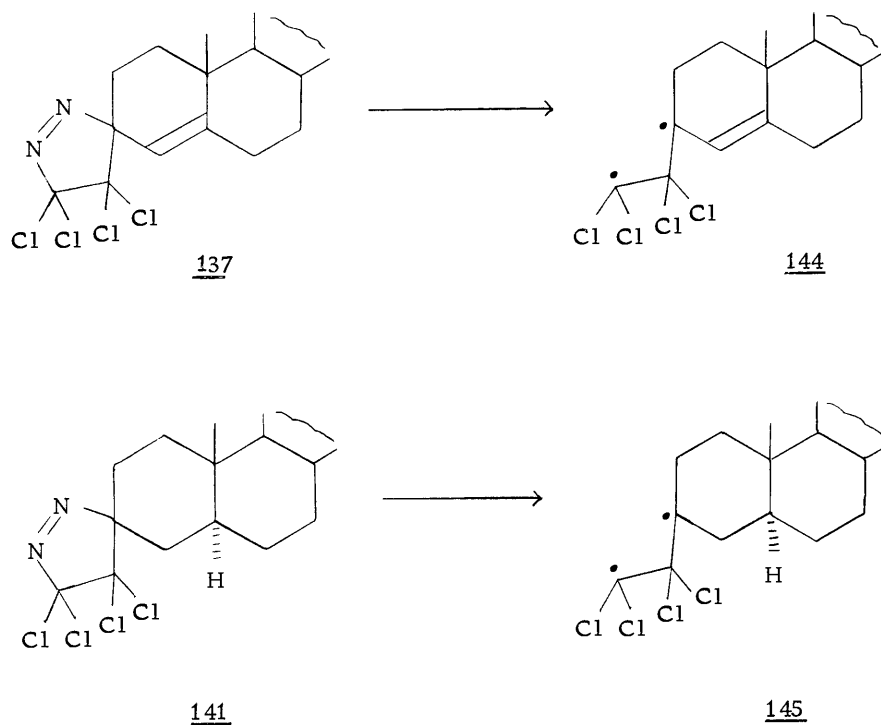
nitrogen more easily than the saturated analog 141 since the diradical

intermediate 144 would be more stable than diradical 145. In any

case, more information is needed to determine the mode of reaction

of 4-cholestenone tosylhydrazone 57 in olefinic solvents. The isola-

tion of 141 represents the first pyrazoline formed from a tosyl-

hydrazone decomposition in an electrophilic olefin. In fact, this is

an area of tosylhydrazone chemistry which is completely unexplored.

Decomposition of 19-Nortestosterone Acetate Tosylhydrazone

146 and Testosterone Tosylhydrazone 148. To be of value in steroid

chemistry, the previously described tosylhydrazone decompositions

should be useful not only in the cholestane series but equally so with

functionalized steroids. In the initial stages of the investigation of

α, β-unsaturated carbene intermediates, 19-nortestosterone acetate

tosylhydrazone 146 and testosterone tosylhydrazone 148 sodium salts

were pyrolyzed in diglyme giving 20% yields of the respective dienes

147 and 148. In hindsight, the yields of dienes might have been

increased by 15-20% by acetylating any hydroxyl group, decreasing

the concentration of the sodium salt in the pyrolysis step and, finally,

using sodium hydride in order to avoid hydrolysis of the acetate

function. Pyrolysis of a dilute solution of 150 with sodium hydride

in tetrachloroethylene gave a 63% yield of the biologically interesting

tetrachloro adduct 151 (NMR shown in Fig. 3).

OAc
H

1) NaOMe
2) Δ, d.g.

OAc
H

146   **147**

OH
H

1) NaOMe
2) Δ, d.g.

OH
H

148   **149**

OAc
H

NaH
Δ, Cl₂C=CCl₂

OAc
H

Cl
Cl
Cl
Cl

150   **151**
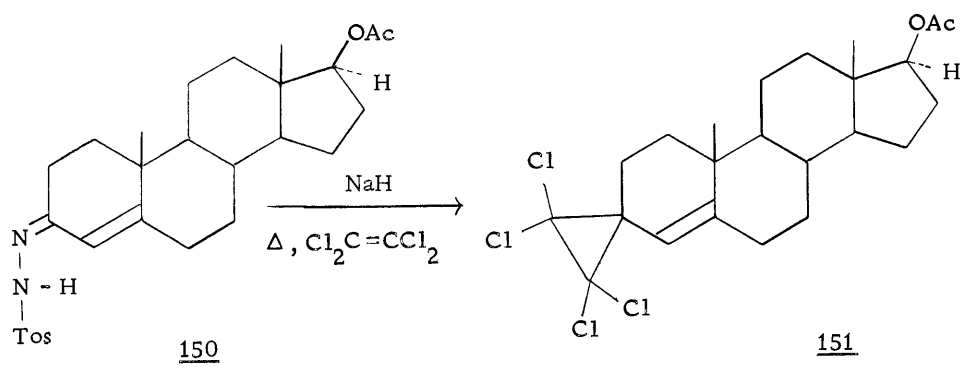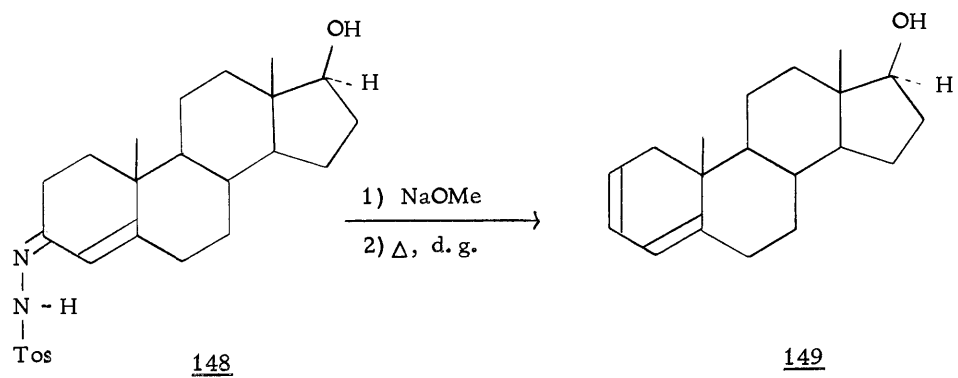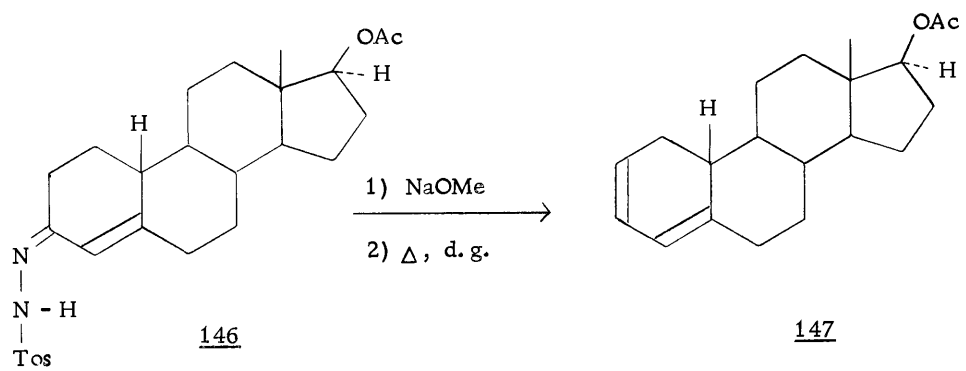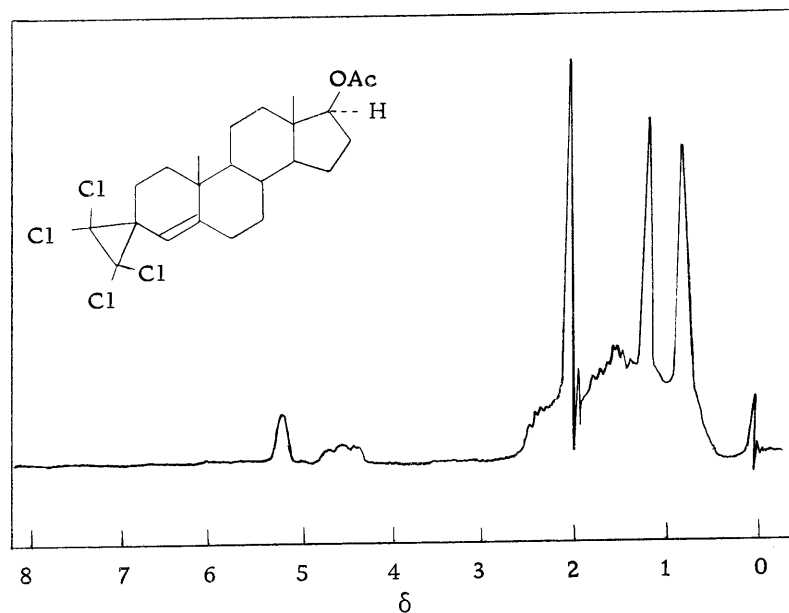
Figure 3. The NMR Spectrum of 151.

Cholesta-2, 4-diene 109 from Butyl Lithium Treatment of 4-

Cholestenone Tosylhydrazone 57. Although reasonable yields of 2, 4-

diene 109 were obtained in the carbene decompositions described in

the previous sections, the material had to be purified by column

chromatography and therefore did not offer the easy synthetic route

which had been sought. After most of this work had been completed,

a different route from tosylhydrazones to olefins was published (115)

involving treatment with excess butyl lithium at low temperature.

The reaction appears to involve removal of an α-hydrogen as indicated

in the Introduction Section. In a preliminary study, application of this

procedure to cholestenone tosylhydrazone 57 gave diene 109 in

greater than 80% yield, isolable as a solid directly from the crude

reaction product. Therefore this reaction is applicable to the

synthesis of dienes. It is interesting to note that no attack occurred

at C-6, as shown by the absence of the 3,5-isomer of 109 in the crude

product. Further study of this route seems justified.

Decomposition of Cholest-1-en-3-one Tosylhydrazone 58 and

Androst-2-en-1-one Tosylhydrazone 159. The detailed study of 4-

cholestenone tosylhydrazone 57 provided intriguing results and it was

of interest to determine whether other A ring α,β-unsaturated

tosylhydrazones would react similarly. Furthermore, for reasons

pointed out in the Introduction Section, the products from such

tosylhydrazones should be of biological interest. Consequently, the

ketone precursors for α,β-unsaturated tosylhydrazones 58 and 159

were synthesized by the route shown in Scheme 3. Pyrolysis of
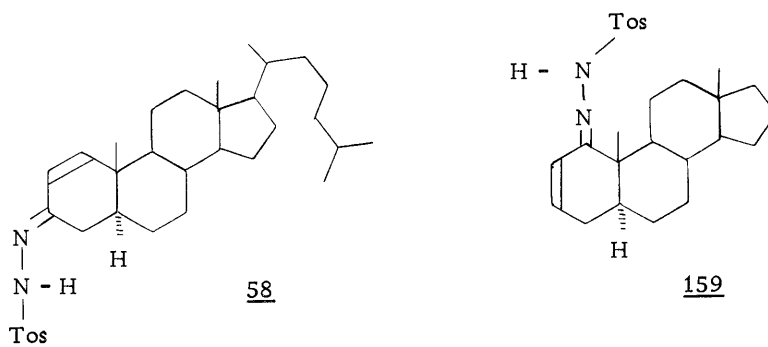
cholest-1-en-3-one tosylhydrazone 58 in dilute solutions of benzene

gave products quite similar to those from 4-cholestenone tosyl-

hydrazone 57. This reaction afforded 1,3-cholestadiene 152 (35%),

spirotropilidene 153 (48%), cholest-1-en-3α-ol-3-methyl ether 154

(8%), and cholest-1-en-3β-ol-3-methyl ether 155 (4%). Use of

sodium hydride, instead of sodium methoxide, gave a mixture con-

taining 23% of 1,3-cholestadiene 152 and 29% of the spiroheptatriene

153. 1,3-Cholestadiene 152 was easily identified by its character-

istic ultraviolet and NMR spectra (Fig. 4).

Scheme 7
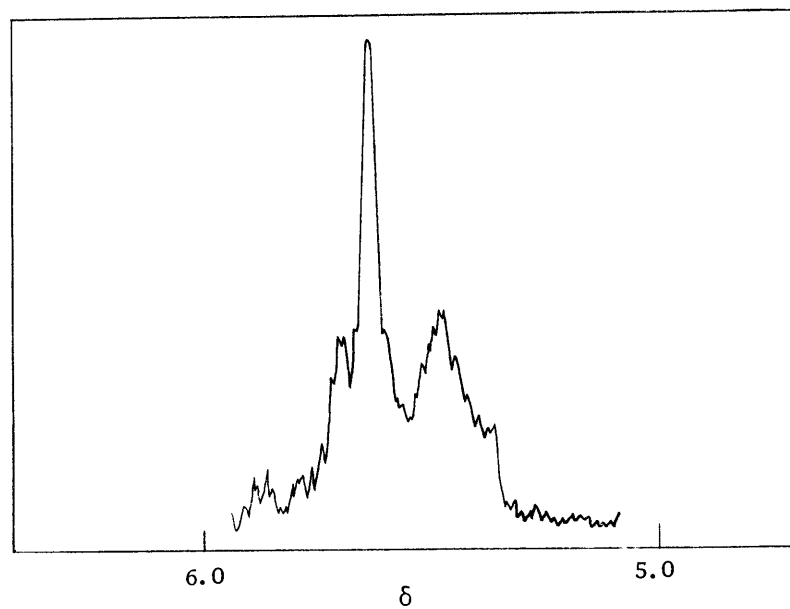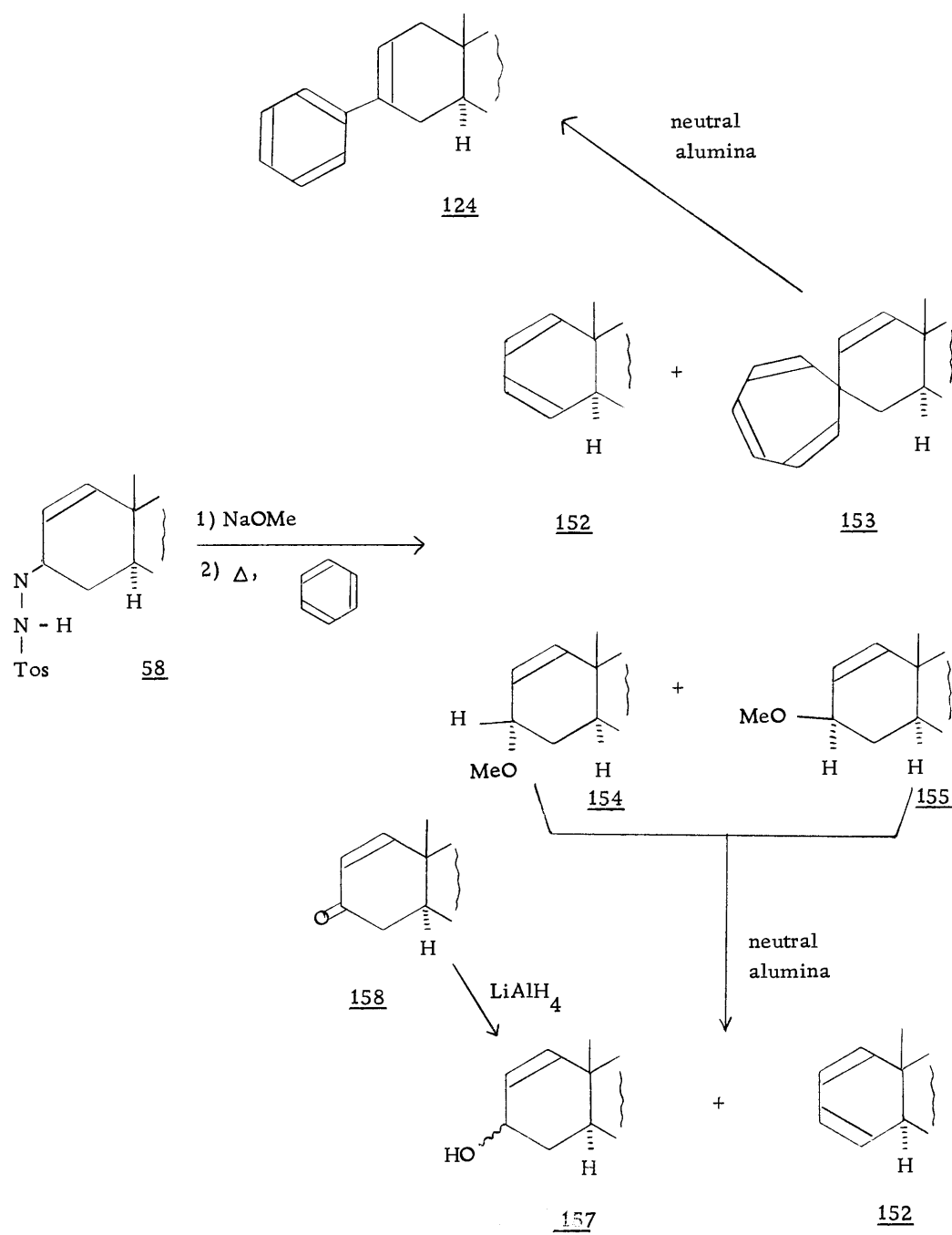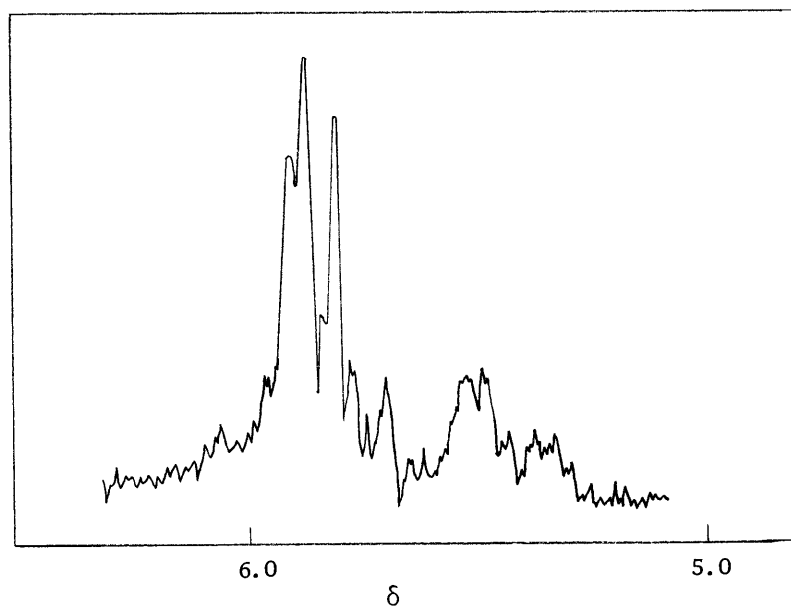
Figure 4. Olefin Band of the NMR Spectrum of 152.
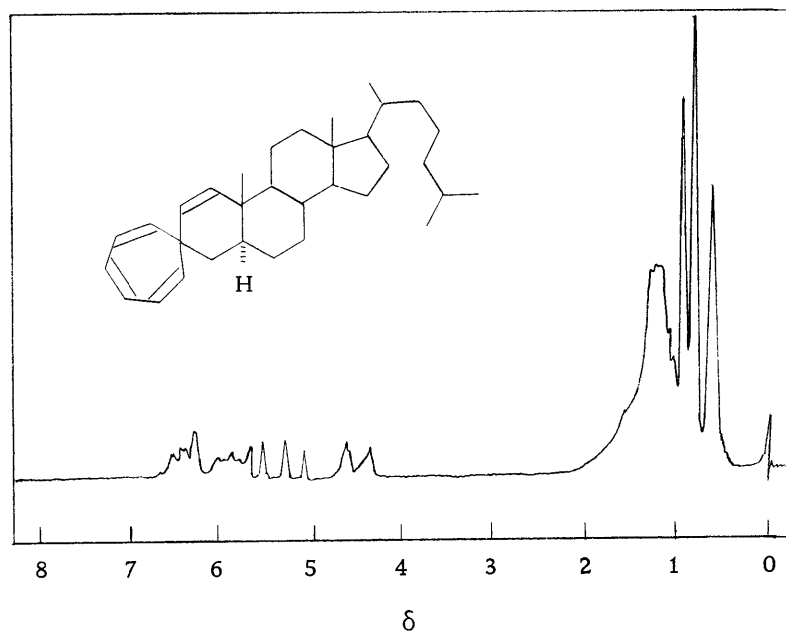
Figure 5. The NMR Spectrum of 153.
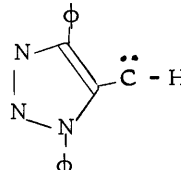
The NMR spectrum of spirotropilidene $\underline{153}$ showed its C-1 and C-2

olefinic protons as an AB quartet in good accord with the assigned

structure (Fig. 5). The methyl ethers $\underline{154}$ and $\underline{155}$ reacted on

neutral alumina affording a mixture of approximately 10% 1, 3-

cholestadiene $\underline{152}$ and 84% of a mixture of the epimeric alcohols $\underline{157}$.

This mixture gives an infrared spectrum which shows all the bonds

of an authentic sample of the epimeric alcohols synthesized by

lithium aluminum hydride reduction of cholest-1-en-3-one $\underline{158}$.

Spirotropilidene $\underline{153}$ readily aromatized on neutral alumina affording

3-phenyl-cholest-2-ene $\underline{124}$.

Decomposition of Androst-2-en-1-one tosylhydrazone $\underline{159}$ was

expected to give $1\beta, 10\beta$ methylene-androst-2-ene $\underline{160}$ as a major

product since C-1 is relatively hindered to intermolecular reactions

and γ-insertion seemed a likely process for stabilization of the

carbene intermediate. The cyclopropyl steroid $\underline{160}$ was of special
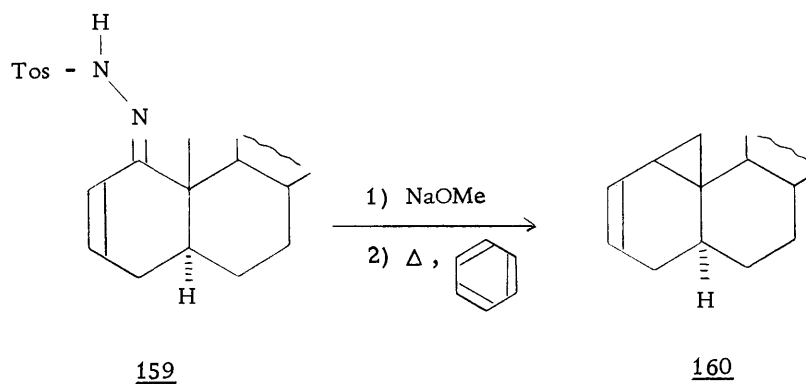
interest since the double bond would provide a site by which this type of steroid could be functionalized at C-3. Pyrolysis of <u>159</u> in diglyme gave a mixture of at least 4 dimers of unknown structure along with an epimeric mixture of methyl ethers and an oil whose NMR spectrum indicated it was a mixture of products resulting from C-H insertion into the solvent. When this decomposition was carried out in benzene, cyclosteroid <u>160</u> was obtained in 16% yield. An additional hydrocarbon product remains unidentified and does not show spectral properties expected for a tropilidene. The NMR spectrum of <u>160</u> shows only one methyl resonance and a multiplet centered at 5.65δ, and the ultraviolet spectrum shows no maximum above 207 mμ. The polar products from this reaction were not examined. The low yield of cyclopropyl steroid <u>160</u> was surprising, but examination of molecular models indicates that possibly the conformation of ring A is not favorable for γ-insertion.

Decomposition of 7-Keto-cholesteryl-acetate tosylhydrazone <u>54</u>.

Caglioti's report (16) that sodium hydride decomposition of 7-keto-cholesteryl acetate tosylhydrazone <u>54</u> in toluene gave 7-dehydro-cholesteryl acetate <u>55</u> in 80% yield seemed at odds with the results obtained from A-ring α,β-unsaturated tosylhydrazones. Repetition of this reaction under the prescribed conditions provided the excellent yield reported in the literature. Since sodium hydride has been reported to give elimination reactions with tosylhydrazones as

well as carbene generation, this decomposition was studied in

various solvent systems with sodium methoxide as base. The sodium

salt of 54 was pyrolyzed in diglyme, benzene, and tetrachloroethylene.

In each of these cases, 7-dehydro-cholesteryl acetate 55 and 7-

dehydro-cholesterol 161 were the major products while products

resulting from attack on solvent were not observed. It is apparent
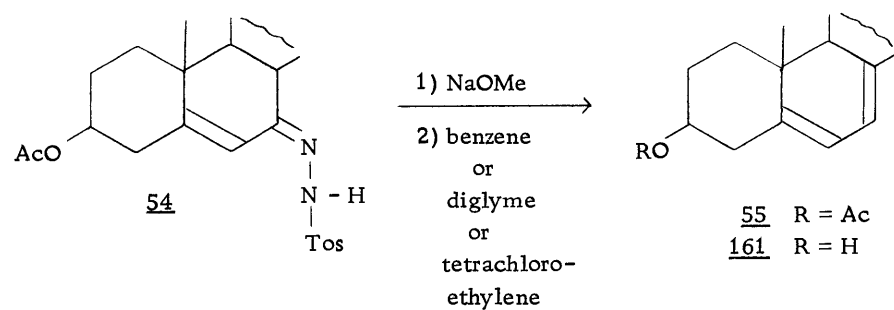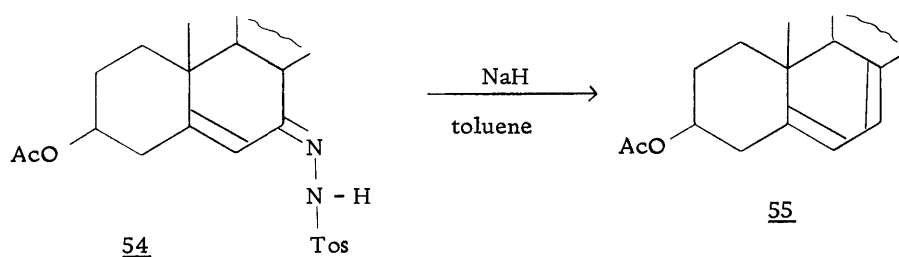
from the studies of cyclic β-alkenyl carbenes <u>108</u>, <u>162</u>, <u>163</u> and <u>164</u>

that intermolecular attack on benzene requires a stabilized carbene

which is not sterically hindered. Unhindered carbene intermediates

<u>108</u>   <u>162</u>   <u>163</u>   <u>164</u>
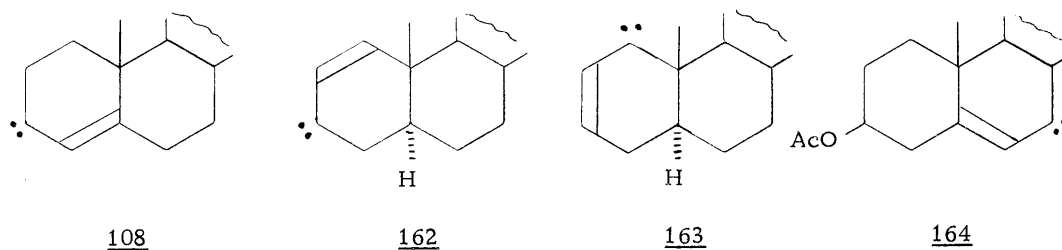
<u>108</u> and <u>162</u> readily added to benzene while the sterically hindered

intermediates <u>163</u> and <u>164</u> did not, but instead reacted intramolecularly.

Further studies on model systems are needed in order to determine

the scope of intermolecular reactions of cyclic β-alkenyl carbenes.

Within the area of steroid chemistry, however, this type of reaction

should be of value in that it makes available a class of spirocyclo-

propylsteroids which was previously unknown.

Decomposition of 16-Dehydro-pregnenolone Tosylhydrazone <u>167</u>

and 16-Methyl-16-dehydro-pregnenolone acetate Tosylhydrazone <u>173</u>

The cyclic β-alkenyl carbenes previously discussed were, for steric

reasons, incapable of forming cyclopropenes by intramolecular

addition. Since the β-alkenyl carbene intermediate <u>77</u> from a 16-

dehydro-20-one steroid tosylhydrazone might afford cyclopropene

<u>165</u> and/or diene <u>166</u>, this system was studied. Pyrolysis of

Scheme 8

Scheme 8
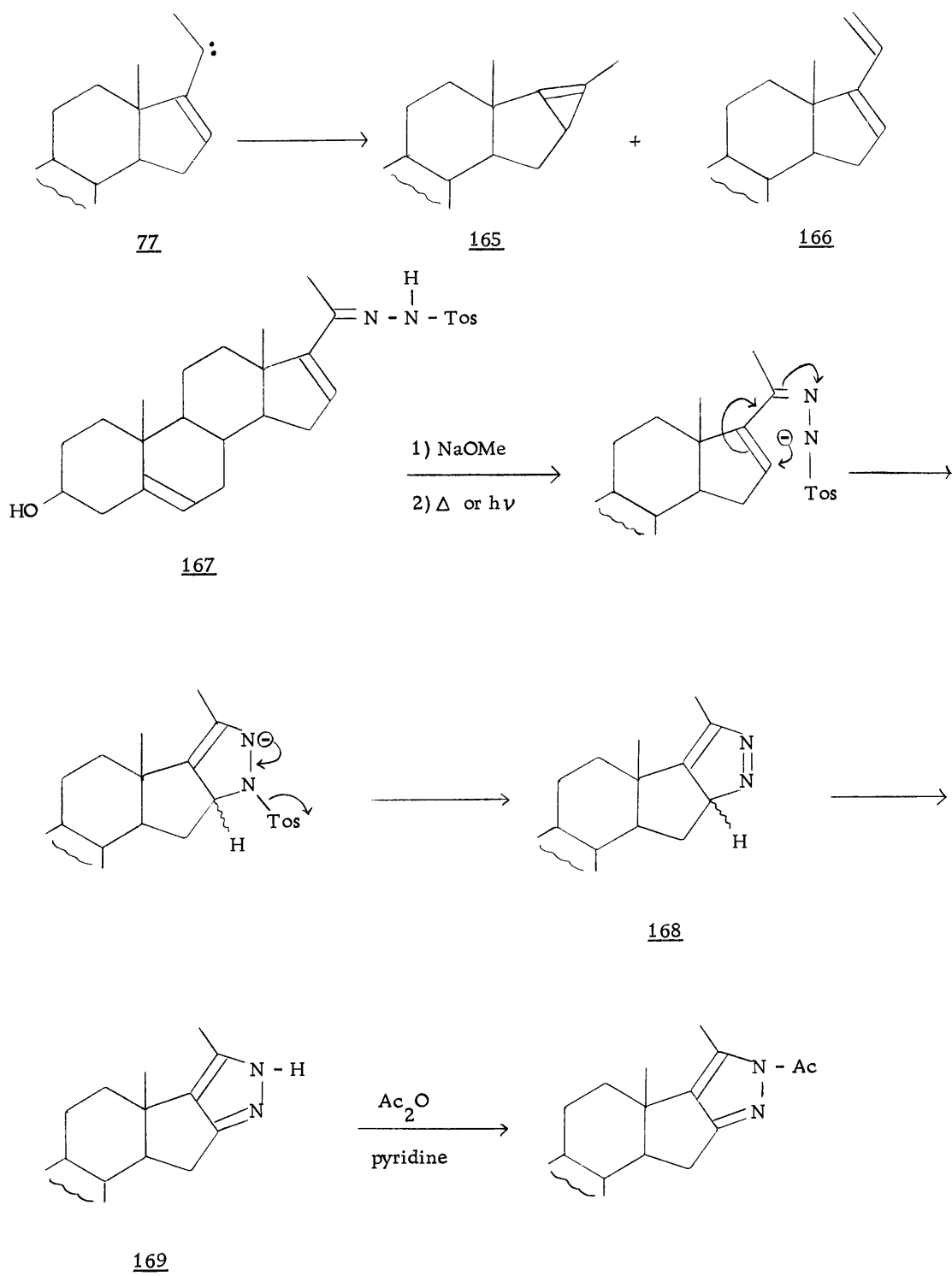
16-dehydro-pregnenolone tosylhydrazone $\underline{167}$ afforded pyrazole $\underline{169}$

in 57% yield. The remaining material was a complex mixture which

was not analyzed. A logical route to [16, 17-C] (5'-methyl)

pyrazolandrost-5-ene-3β-ol $\underline{169}$ involves intramolecular addition of

the anion of the tosylhydrazone (scheme 8), or intramolecular addition

from the diazo intermediate to the 16-double bond. The initially

formed pyrazolenine $\underline{168}$ then tautomerizes to $\underline{169}$. Formation of such

a pyrazole is in good agreement with studies made on a similarly sub-

stituted tosylhydrazone $\underline{170}$ which gave only 1.5% of a cyclopropene

product (29). Closs et al. (27) reported that pyrazolenine $\underline{171}$ was

$\underline{170}$

$\underline{171}$ $\underline{172}$
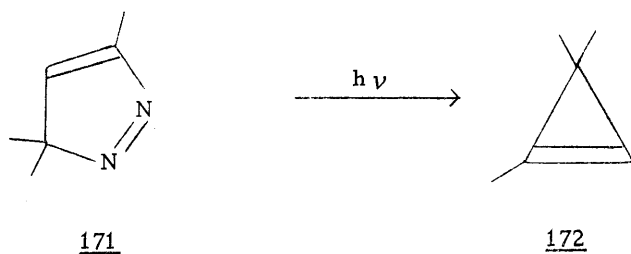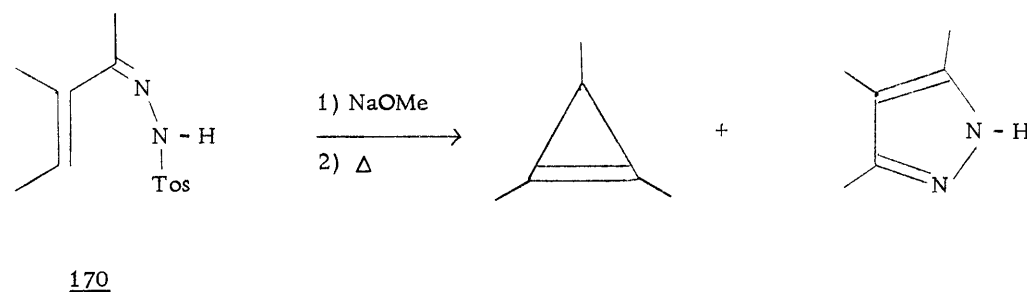
photolytically converted to cyclopropene 172. This reaction

encouraged the photolytic study of 16-dehydropregnenolone tosyl-

hydrazone 167. It was hoped that the transient pyrazolenine 168 would

decompose faster than it could tautomerize to the pyrazole. Unfor-

tunately, the major product was again pyrazole 169.

16-Methyl-16-dehydro-pregnenolone acetate tosylhydrazone 173

was selected for decomposition study since the added substituent at

C-16 might allow carbenic decomposition to occur faster than

heterocycle formation, or, if a heterocycle was formed, it would be

unable to tautomerize. Pyrolysis of 173 in diglyme, followed by

normal work-up procedure gave a solid mass of low solubility.

Acetylation of this material gave a product identified as the hydroxy-

diacetate 174. This structural assignment was based on elemental

analysis and spectral data. The physical properties of 174 indicate

only one isomer is present though the stereochemistry of the ring

juncture is not known. Pyrazolenine 175 was suspected as an inter-

mediate in this reaction. Use of sodium hydride and glyme in the

decomposition step followed by removal of the solvent in vacuo

allowed isolation of pyrazolenine 175 (47% yield). An additional

product of this reaction remains unidentified. Pyrazolenine 175 was

Scheme 9
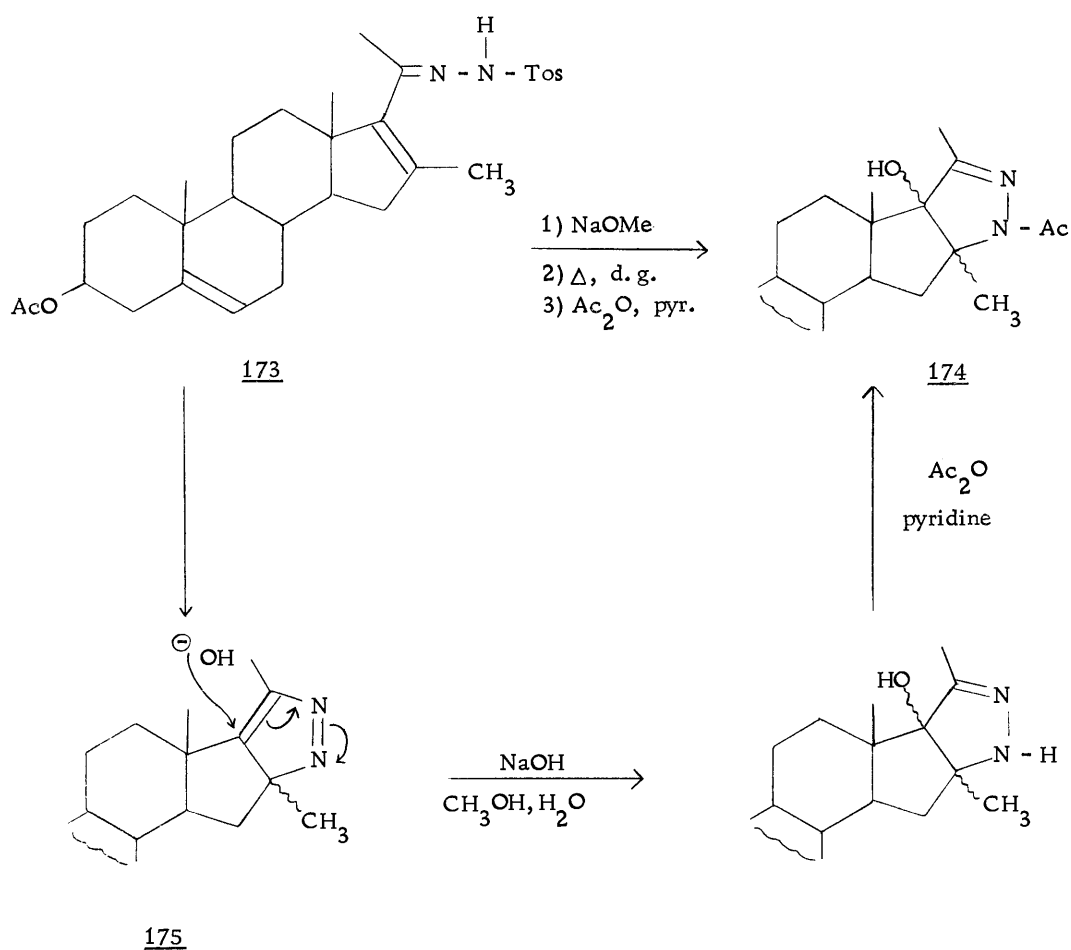
identified from its elemental analysis and spectral data (NMR shown

in Fig. 6). Treatment of pyrazolenine 175 with methanol, water,

and sodium hydroxide, followed by acetylation afforded the hydroxy-

diacetate 174. The initially formed pyrazolenine evidently under-

goes 1, 4-addition of water upon work up in basic solution. Similar

1, 4-additions to azo compounds 176 and 177 have been reported (7, 18)

recently. The utility of this route to interesting steroid heterocycles

is obvious, and should prove of great ineterest.

176

$$\phi - N - N - H \quad \quad H$$
$$\quad\quad | \quad\quad |$$
$$H \quad\quad H$$

$$CH_3 \quad\quad R$$
$$C = C$$
$$\quad\quad H$$
$$N$$
$$\|$$
$$N$$
$$C - NH_2$$
$$\|$$
$$O$$

177

HCl

$$CH_3 \quad Cl$$
$$C - CHR$$
$$N$$
$$\|$$
$$N - C - NH_2$$
$$| \quad\quad \|$$
$$H \quad\quad O$$

AcO

H

δ
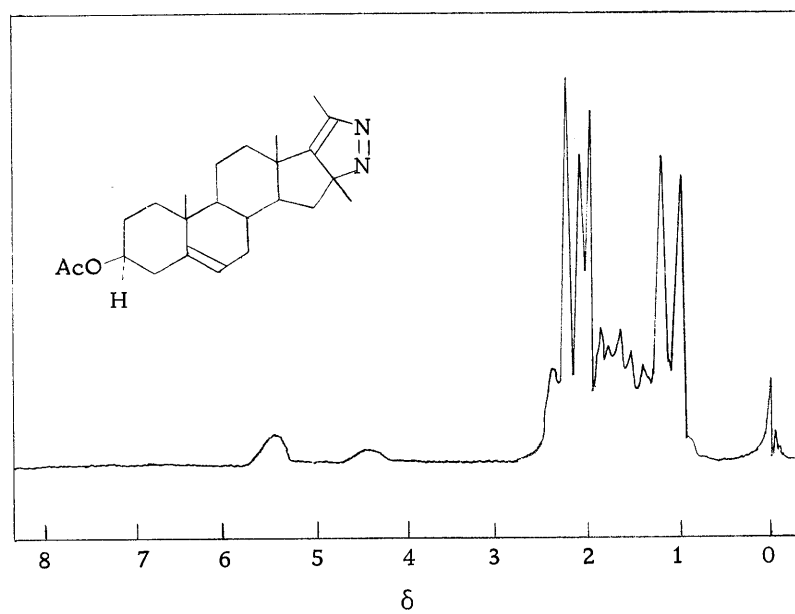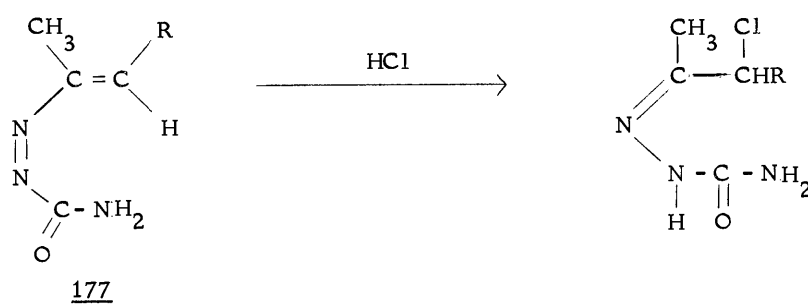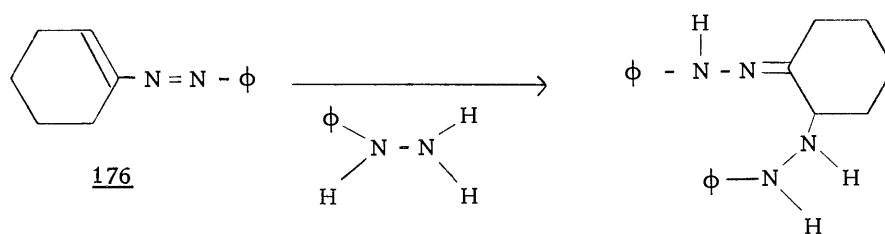
Figure 6. The NMR Spectrum of 175.

Rearrangements of Spirosteroids on Alumina Column

Chromatography. Many of the early frustrations encountered in this

work were due to molecular rearrangements of the initially formed

spirocompounds upon alumina chromatography (Scheme 10). Basic

and neutral alumina (Brinkmann, Activity II) catalyzed all the

transformations shown in Scheme 10. These rearrangements occurred

at room temperature in excellent yield. Acid-washed alumina

catalyzed these transformations only slowly and silica gel did not

cause any rearrangement. In fact, silica gel could be used very

successfully in separations of these spirosteroids. On the basis of

this information and the fact that neutral alumina normally gives

basic reactions (19), a base-catalyzed mechanism for these facile

rearrangements is more attractive than an acid-catalyzed one. A

base-catalyzed mechanism for 153 is shown in Scheme 11 and should

also be applicable to 116, 132 and 133. Structure 176 is tentative

since the stereochemistry of the ring juncture is based on expected

axial protonation of a carbanion at C-5. The position of the double

bond in 176 is assigned to the Δ-2 position by analogy with 124. A

base-catalyzed rearrangement of 136 and 141 is also quite feasible.

The electron withdrawing power of the halogenated rings might

acidify the C-2 protons, thus facilitating their removal by base

(Scheme 12).

Scheme 10

116 → (Al$_2$O$_3$) → 124

153 → (Al$_2$O$_3$) → 124

132 or 133 → (Al$_2$O$_3$) → 176

136 → (Al$_2$O$_3$) → 177

141 → (Al$_2$O$_3$) → 48

Scheme 11

153

Scheme 12

136

B:

177
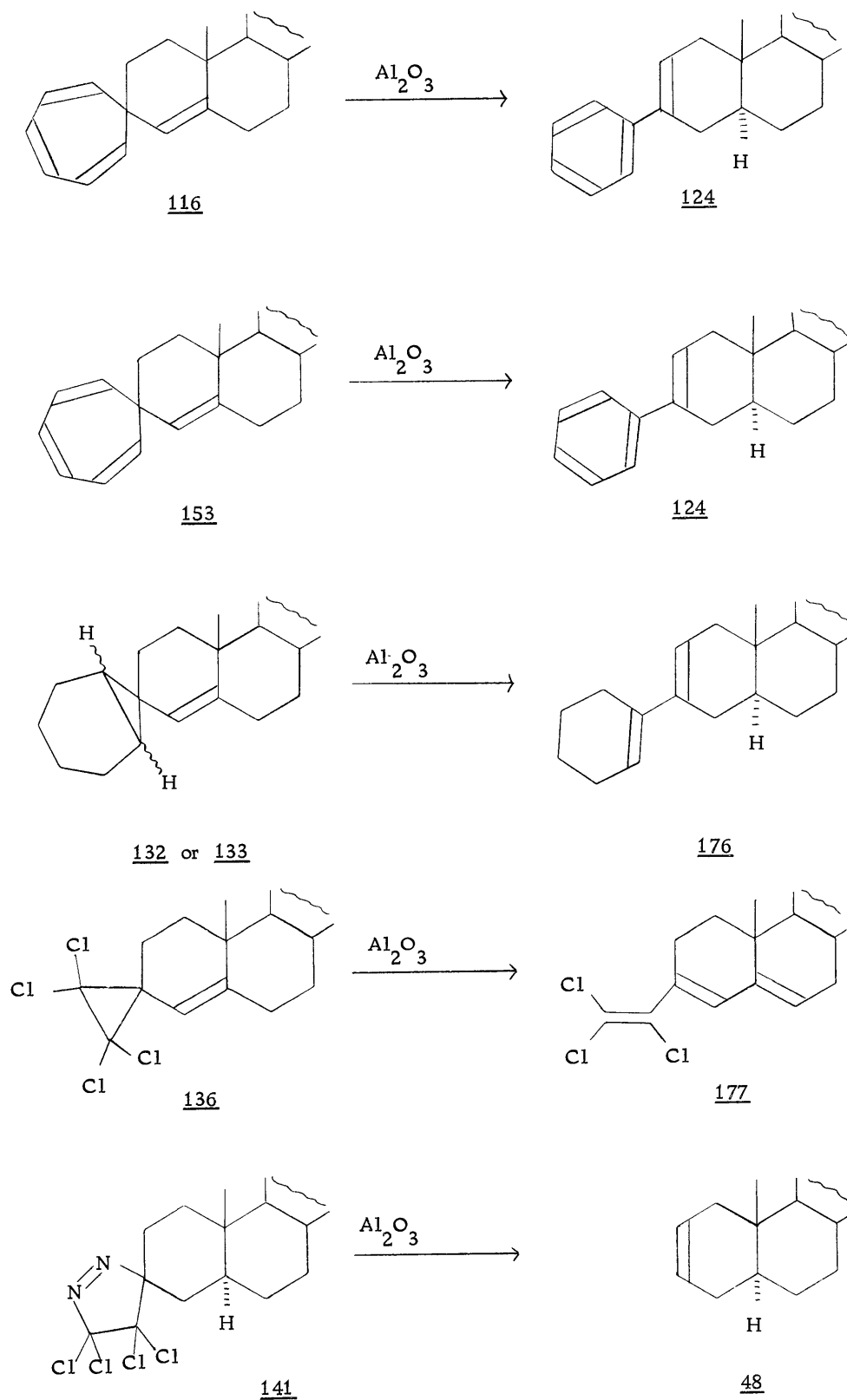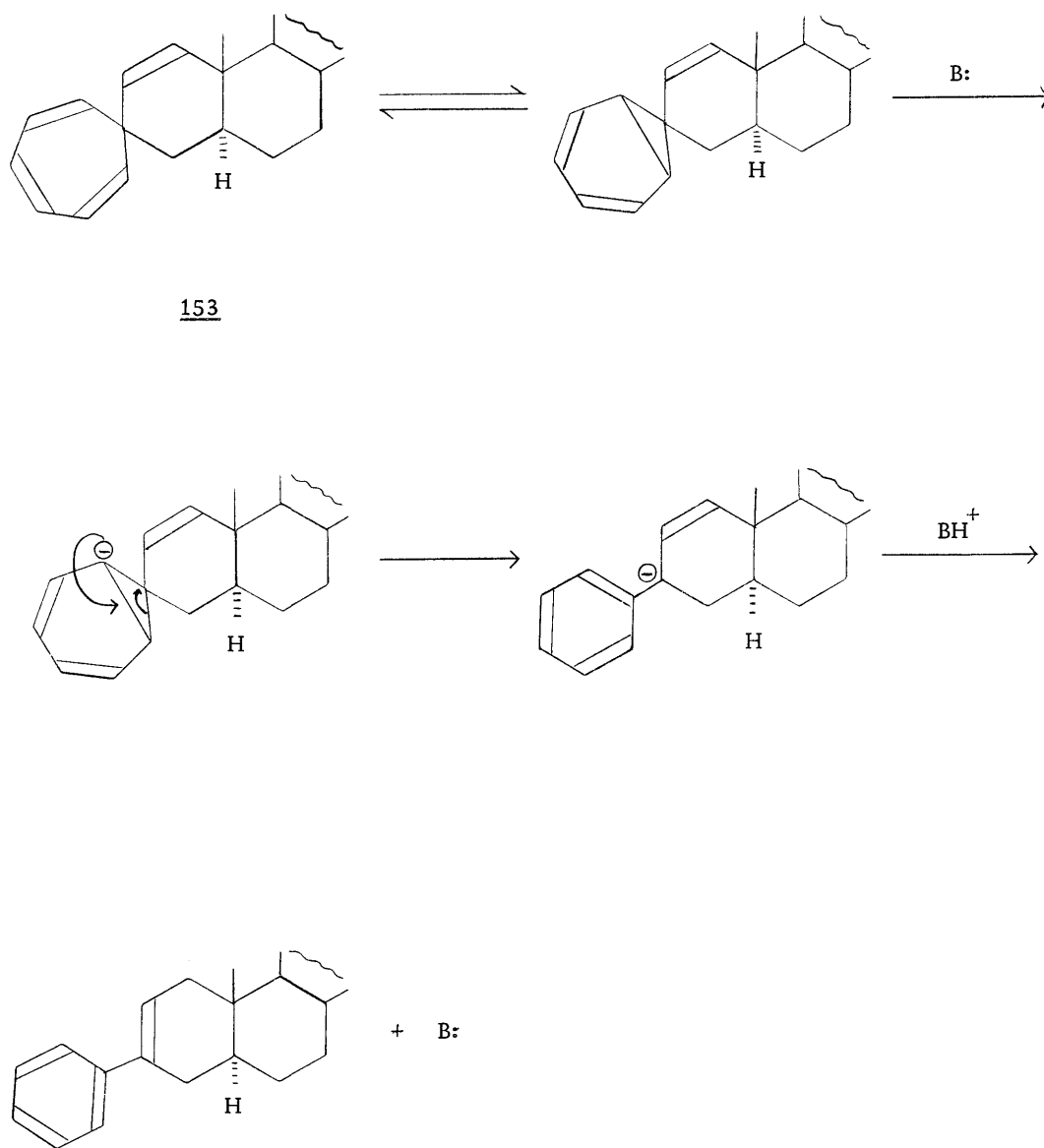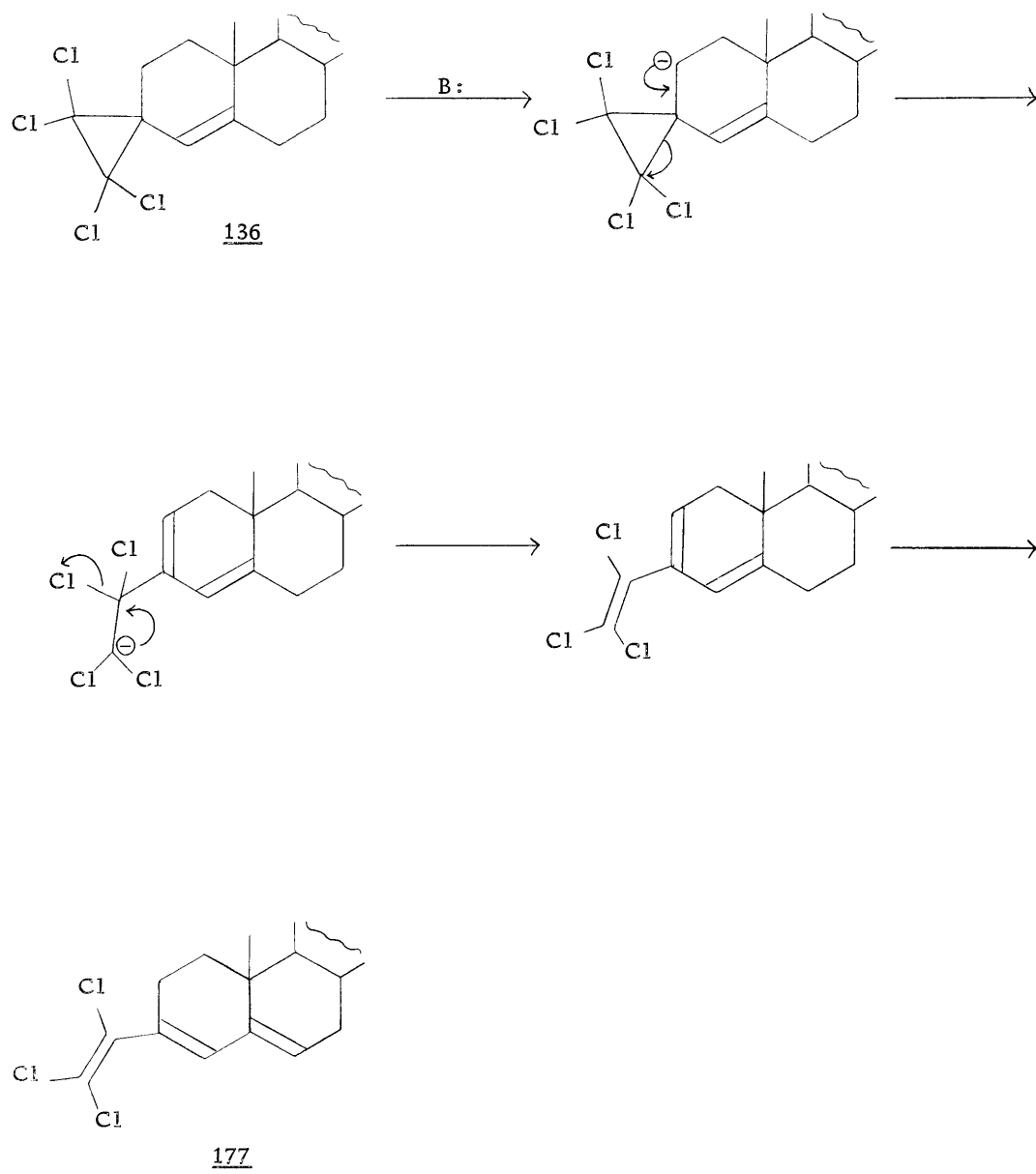
Conclusions

The synthetic utility of both saturated and α,β-unsaturated steroid tosylhydrazones has been thoroughly investigated. Carbenic type decompositions of the latter lead to previously unsuspected solvent-derived products, suggesting increased stability of the intermediates. A method of easily separating the complex products has been developed and allowed a study of the effect of reaction conditions on the decompositions. Routes to steroid homoannular dienes, spirocompounds, and fused pyrazoles have been developed. The biological activity of these compounds will be evaluated soon.

EXPERIMENTAL

All melting points were recorded on a Buchi melting point apparatus and are corrected. The analyses were performed by Galbraith Laboratories, Inc., Knoxville 21, Tennessee. Infrared absorption spectra were determined using a Beckman IR-8 spectrometer. Ultraviolet absorption spectra were measured in cyclohexane or methanol with a Beckman DB or Cary 15 recording spectrometer. Proton nuclear magnetic resonance spectra (NMR) were run in carbon tetrachloride or deuterochloroform on a Varian Model A-60 instrument. Optical rotations were run on ca. one percent solutions in chloroform using a Perkin-Elmer P22 spectropolarimeter. Thin layer chromatographies were run on Brinkmann silica gel G plates unless otherwise stated. Silver nitrate impregnated silica gel chromatography plates were prepared by spraying a silica gel G plate lightly and evenly with a 10% solution of silver nitrate and then drying at 90° for 40 minutes. Silver nitrate impregnated silica gel for column chromatographies was prepared by adding a concentrated solution of silver nitrate (10% of absorbent weight) to silica gel H. This mixture was shaken for ca. 1 hour and then dried overnight at 90°. Percentages of compounds are reported as weight-percentages of the product mixtures. All tosylhydrazone decompositions were run under a nitrogen atmosphere. "Formation of the

sodium salt in the usual manner" means that a methanol solution of

sodium methoxide and tosylhydrazone was stirred at room tempera-

ture for ca. 20 minutes followed by removal of methanol in vacuo

and further drying of the sodium salt for 15 hours at 0.05 mm. in a

chamber equipped with phosphorous pentoxide. "Worked-up in the

usual way" means the organic reaction mixture was poured into a 5%

solution of hydrochloric acid, washed with water and dried over

magnesium sulfate.

5-Androstene-3β-ol-17-one p-Toluenesulfonylhydrazone 78.

To a solution of 7.0 g. (0.037 mole) of p-toluenesulfonhyhydrazine

in 150 ml. of methanol was added 10.0 g. (0.035 mole) of dehydro-

epiandrosterone. After the resulting solution had been heated under

reflux for two hours, the methanol was removed in vacuo. The crude

product was recrystallized from ethyl acetate affording 13.0 g. of

product, m.p. 170-174° (dec.). A further recrystallization from

ethyl acetate provided the analytical sample, m.p. 172-174° (dec.),

$\alpha \vert_D$ - 17°.

      Anal. Calcd. for $C_{26}H_{36}N_2O_3S$: C, 68.39; H, 7.95; N, 6.14

      Found: C, 68.46; H, 7.86; N, 6.26

The infrared spectrum shows a weak band at 3220 cm^{-1} (N-H

stretch); a weak band at 1590 cm^{-1} (aromatic skeletal vibration); and

strong bands at 1340 cm^{-1} and 1160 cm^{-1} (characteristic of $-SO_2-$).

Pyrolysis of 5-Androstene-3β-ol-17-one p-Toluenesulfonyl-

hydrazone 78 with Sodium Methoxide in Diglyme. To 150 ml. of

anhydrous methanol was added 0.68 g. (0.030 mole) of clean sodium

followed by 13.4 g. (0.030 mole) of dehydroepiandrosterone tosyl-

hydrazone. After the solution had been stirred for one-half hour, the

methanol was removed in vacuo. The residual salt was broken up and

dried overnight at 0.05 mm. Anhydrous diglyme (ca. 200 ml.) was

distilled onto the sodium salt and the solution was heated under reflux

until nitrogen evolution had stopped. The cooled solution was added

to ice-water and extracted with ether. The combined ether layers

were washed with 5% hydrochloric acid and with several 50 ml. por-

tions of water, and then dried over magnesium sulfate. Removal of

the ether in vacuo afforded 8.02 g. of white solid. Thin layer

chromatography indicated one predominant product (R_f 0.50;

ethyl acetate-benzene, 2:1), but thin layer chromatography on silica

gel impregnated with silver nitrate showed two products (R_f 0.42 and

0.23; benzene-ethyl acetate, 1:1). Chromatography of this material

on 240 g. of silica gel impregnated with silver nitrate provided 5.48 g.

(68%) of a white solid, (Benzene-ethyl acetate, 9:1, fractions 3

through 6), and 1.36 g. (17%) of a crystalline solid (methanol,

fractions 15 through 19).

Recrystallization of the major product from acetone-hexane

gave white crystalline material, m.p. 122-124°. Sublimation at

80° and 0.05 mm. provided the analytical sample, m. p. 123-124°,

$\alpha]_D$ -63°.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36

Found: C, 83.67; H, 10.45

The infrared spectrum shows bands at 3630 cm^{-1}, 3050 cm^{-1},

and 1005 cm^{-1}. The NMR spectrum displays a broad band at 5.30 δ,

one sharp band at 60 c.p.s. due to an angular methyl group, a

triplet centered at 0.3δ and a quartet at 0.0δ consistent with 13β, 17β-

methylene-androst-5-ene-3β-ol 79.

The minor product was identified as 5, 16-androstadiene-3β-ol 80

and recrystallization from acetone-hexane gave 1.03 g. of fine

needles, m.p. 134-137°. Sublimation at 80° and 0.07 mm. afforded

a white solid, m.p. 136-138° [lit. (4) m.p. 140-141°] .

The infrared spectrum shows significant bands at 3630 cm^{-1}

and 1665 cm^{-1}. The NMR spectrum shows a multiplet at 5.8δ (2H),

a broad band at 5.4δ (1H), a broad band at 3.5δ (1H) and sharp bands

at 63 c.p.s. (19-Me) and 48 c.p.s. (18-Me).

Pyrolysis of 5-Androstene-3β-ol-17-one p-Toluenesulfonyl-

hydrazone 78 with Varying Amounts of Sodium Methoxide in p-Xylene.

Mixtures of 5-androstene-3β-ol -17-one tosylhydrazone and sodium

methoxide, varied between 0.5 equivalents and 5.0 equivalents, were

used in the usual way to form the sodium salt of the tosylhydrazone.

In each case, ca. 100 ml. of p-xylene was added per gram of

tosylhydrazone. These mixtures were then heated under reflux until
nitrogen evolution ceased. The cooled solutions were worked-up in
the usual manner affording a solid which gave on thin layer chromatog-
raphy one predominant band (R_f 0.47; benzene-ethyl acetate, 1:1).
Column chromatography on silica gel gave, on elution with benzene-
ether, 8:1, (fractions 4 through 6), the material corresponding to the
predominant band observed on thin layer chromatography. Thin
layer chromatography on silica gel impregnated with silver nitrate
showed that this major fraction from each reaction gave two bands
(R_f 0.42, 0.23; benzene-ethyl acetate, 1:1). NMR spectra were
made for each of the major fractions of each reaction. The NMR
spectra of fractions from reactions employing 1 equivalent or more
of sodium methoxide showed the same bands as the NMR spectrum
of an authentic mixture of 13β,17β-methylene-antrost-5-ene-3β-ol
79 and 5,16-androstadiene-3β-ol 80. These NMR spectra show
broad bands at 5.8δ (C-16,17 olefinic protons), 5.4δ (C-6 olefinic
proton), 3.5δ (3α-proton), and 0.3δ and 0.0δ (cyclopropyl protons),
and sharp bands at 63 c.p.s. (19-Me of 80), 60 c.p.s. (19-Me of 79)
and 47 c.p.s. (18-Me of 80).

The NMR spectrum of the fraction coming from the reaction
utilizing 0.5 equivalents shows, in addition to the bands described
for a mixture of 5,16-androstadiene-3β-ol 80 and 13β,17β-methylene-
androst-5-ene-3β-ol 79, a strong sharp band at 56 c.p.s. due to an

unidentified product or products.

The relative amounts of products in each case were determined from integration of the representative bands. In order to check the validity of the integration, the NMR samples were mixed with deuterium oxide so that the band arising from the hydroxyl function did not overlap with the band at 3.5 δ due to the 3α-proton. The results of these experiments are summarized in Table 25.

In the reaction which utilized 2.0 equivalents of sodium methoxide, a careful NMR analysis was made of all fractions from the column chromatography. The NMR spectra showed no absorption bands which might be expected for a product arising from inter-molecular attack of the generated carbene on p-xylene.

13β,17β-Methylene-androstane-3β-ol 88. A solution of 2.24 g. (0.008 mole) of 13β,17β-methylene-androst-5-ene-3β-ol, 250 ml. of methanol, and 0.75 g. of 10% Pd/C catalyst was hydrogenated over-night on a Parr low pressure apparatus.

The hydrogenation was begun at a pressure of 45 lb. p.s.i. and fell to a constant pressure of 39.5 lb. p.s.i. The catalyst was removed by three gravity filtrations. Removal of the solvent in vacuo afforded a white solid. This material was recrystallized from acetone-hexane, m.p. 150-152° [lit. (15), m.p. 153-155°].

The infrared spectrum displays significant bands at 3050 cm^{-1} and 1005 cm^{-1}.

Table 25. NaOMe Treatment of Tosylhydrazone 78.

Grams of Tosylhydrazone 78	Equiv. NaOMe	79/80	C-6H C-3αH	Other Products (% of Major Band)	Yield of Major Fraction
2.0	0.5	2.0	0.9	54%	0.373 g. (63%)
1.0	1.0	3.1	1.0	---	0.480 g. (81%)
1.8	2.0	2.0	0.9	---	0.676 g. (63%)
1.0	5.0	2.0	1.0	---	0.391 g. (66%)

Photolysis of 5-Androstene-3β-ol-17-one p-Toluenesulfonyl-hydrazone 78 with Sodium Methoxide in Tetrahydrofuran. To 150 ml. of anhydrous methanol was added 0.51 g. (0.022 mole) of sodium followed by 10.0 g. (0.022 mole) of dehydroepiandrosterone. After removal of the solvent and drying of the residual salt overnight at 0.05 mm., 1.2 l. of anhydrous tetrahydrofuran was added. This solution was irradiated for 6 hours. The sodium p-toluenesulfinate precipitate was filtered off, and the tetrahydrofuran was removed in vacuo affording 6.70 g. of a yellow solid. Column chromatography of this material on acid-washed alumina gave 6.1 g. of white solid (benzene-ether; 4:1) which was shown by thin layer chromatography to be a mixture of 79 and 80. Column chromatography 150 g. of silica gel impregnated with silver nitrate gave 3.39 g. (57%) of 13β,17β-methylene-androst-5-ene-3β-ol 79 and 1.36 g. (23%) of 5,16-androstadiene-3β-ol 80.

5α-Androstane-3β-ol-17-one. A solution of 5.0 g. (0.017 mole) of dehydroepiandrosterone, 250 ml. of anhydrous ethanol and 1.0 g. of 10% Pd/C catalyst was hydrogenated overnight on a Parr low pressure apparatus.

The hydrogenation was begun at 45 lb. p.s.i. and fell to a constant pressure of 43 lb. p.s.i. The catalyst was removed by three gravity filtrations. Removal of the ethanol in vacuo afforded a white solid. This material was recrystallized from aqueous methanol,

m. p. 173-175° [lit. (44), m. p. 175°].

5α-Androstane-3β-ol-3-acetate-17-one p-Toluenesulfonyl-

hydrazone 86. To a solution of 5.0 g. (0.017 mole) of 5 α-androstane-

3β-ol-3-acetate-17-one in 150 ml. of methanol was added 3.2 g.

(0.017 mole) of p-toluenesulfonylhydrazine. After the resulting

solution had been heated under reflux for two hours, the methanol

was removed in vacuo. The initial product was recrystallized from

acetone affording 5.8 g. of a granular solid, m. p. 179-184° (dec.).

[Lit. (15) gives no m. p.].

Anal. Calcd. for $C_{28}H_{40}N_2O_4S$: C, 67.17; H, 8.05; N, 5.60

Found: C, 67.21; H, 8.01; N, 5.71

The infrared spectrum shows bands at 3220 cm^{-1}, 1340 cm^{-1},

and 1160 cm^{-1}.

Pyrolysis of 5α-Androstane-3β-ol-3-acetate-17-one p-

Toluenesulfonylhydrazone 86 with Sodium Methoxide in Diglyme. To

50 ml. of anhydrous methanol was added 0.18 g. (0.0085 mole) of

sodium followed by the addition of 4.20 g. (0.0085 mole) of androstane-

3β-ol-3-acetate-17-one tosylhydrazone. After the solution had been

stirred for one-half hour, the methanol was removed in vacuo. The

residual salt was broken up and dried overnight at 0.05 mm.

Anhydrous diglyme (100 ml.) was distilled onto the sodium salt and

the solution was heated under reflux until nitrogen evolution ceased.

The cooled solution was added to ice-water and extracted with ether. The organic layers were washed with 5% hydrochloric acid and several 25 ml. portions of water, and dried over magnesium sulfate. Removal of the ether in vacuo afforded 1.60 g. of white solid. Thin layer chromatography indicated one product (R_f 0.68; ethyl acetate-benzene, 1:1). Thin layer chromatography on silica gel impregnated with silver nitrate showed two predominant components (R_f 0.33 and 0.17; ethyl acetate-benzene, 1:1). Column chromatography of this material on 30 g. of silica gel impregnated with silver nitrate provided 0.98 g. (61%) of white solid, m.p. 150-152° (Benzene-ethyl acetate, 8:1; fractions 1 and 2), and 0.380 g. (24%) of crystalline solid, m.p. 112-120° (methanol; fraction 4).

The major product was identified as 13β,17β-methylene-androstane-3β-ol 88. Sublimation at 80° and 0.07 mm. gave 0.72 g. of fine needles, m.p. 150-152° [lit. (15), m.p. 153-155°].

The infrared spectrum shows bands at 3630 cm^{-1}, 3050 cm^{-1}, and 1005 cm^{-1}. The NMR spectrum shows a broad band at 3.56δ (3α-H), a sharp band at 48 c.p.s. (19-Me), a triplet at 0.26δ and a quartet centered at -0.08δ due to protons on a cyclopropane ring.

The minor product was identified as 16-androstene-3β-ol 89. Sublimation at 80° and 0.05 mm. provided 0.29 g. of a white solid, m.p. 117-121°. An additional recrystallization from acetone-hexane gave a crystalline solid, m.p. 119-122° [lit. (17) m.p. 123°].

The infrared spectrum shows bands at 3630 cm^{-1} and 1665 cm^{-1}.

The NMR spectrum shows a multiplet at 5.75δ (2H), a broad band at

3.56δ (1H) and sharp bands at 50 c.p.s. (19-Me) and 44 c.p.s. (18-

Me).

Cholestan-1-one p-Toluenesulfonylhydrazone I-103. To a

solution of 0.912 g. (0.0024 mole) of cholestane-1-one in ca. 40 ml.

of methanol was added 0.500 g. (0.0026 mole) of p-toluenesulfonyl-

hydrazine and five drops of concentrated hydrochloric acid. The

resulting solution was heated under reflux for three and one-half

hours. Most of the solvent was removed in vacuo. The residue was

dissolved in methylene chloride and washed with 5% sodium bicarbonate

and water and dried over magnesium sulfate. Removal of the

methylene chloride in vacuo followed by trituration of the residue

with methanol gave 0.518 g. of a white solid, m.p. 132-134° (dec.),

$\alpha]_D$ +83°.

Anal. Calcd. for C$_{34}$H$_{54}$N$_2$O$_2$S: C, 73.60; H, 9.81; N, 5.05

Found: C, 73.71; H, 9.81; N, 5.18

The infrared spectrum displays bands at 3220 cm^{-1}, 1590 cm^{-1},

1340 cm^{-1} and 1160 cm^{-1}.

Pyrolysis of Cholestan-1-one p-Toluenesulfonylhydrazone I-103

with Sodium Methoxide in Celite. To 150 ml. of anhydrous methanol

was added 0.062 g. (0.0027 mole) of sodium followed by 1.500 g.

(0.0027 mole) of cholestan-1-one tosylhydrazone. After the solution had been stirred for one-half hour, the methanol was removed _in vacuo_. The residual salt was broken up and dried overnight at 0.05 mm. Celite, 5.0 g., previously washed with hexane and oven dried, was thoroughly mixed with the sodium salt. The resulting mixture was heated at 155° until nitrogen evolution stopped. The celite mixture was poured into ether and stirred for ca. one hour. Removal of the celite by vacuum filtration followed by evaporation of the ether provided 0.819 g. of white solid. Thin layer chromatography on silica gel showed two bands (R_f 0.86 and 0.76; hexane). Thin layer chromatography on silica gel impregnated with silver nitrate indicated two products (R_f 0.86 and 0.06; hexane). Column chromatography of this mixture on 30 g. of silica gel impregnated with silver nitrate gave, on elution with 90 ml. of hexane, 0.036 g. (5%) of a white solid designated as 1β,10β-methylene-cholestane 104. Recrystallization from methanol ether gave 0.021 g. of white plates, m.p. 55-57° [lit. (130), m.p. 57°].

The infrared spectrum shows significant bands at 3050 cm^{-1} and 1010 cm^{-1}. The NMR spectrum shows sharp bands at 55.5 c.p.s. and 50 c.p.s. (26- and 27-Me), and 37 c.p.s. (18-Me), and broad bands at 0.3δ and 0.0δ.

Elution with 90 ml. of 2:1 hexane-benzene afforded 0.772 g. (95%) of an oily solid shown to be 1-cholestene 105. Recrystallization

from acetone gave 0.580 g. of needles, m.p. 67-69°, $\alpha]_D$ +13°

[lit. (44) m.p. 70°, $\alpha]_D$ +13°].

The infrared spectrum shows bands characteristic of 1-cholestene at 748 cm^{-1}, 718 cm^{-1} and 700 cm^{-1}.

Cholestan-3β-ol I-95. A solution of 10.0 g. (0.026 mole) of cholesterol, 250 ml. of ethyl acetate, 3 drops of perchloric acid and 0.3 g. of platinum oxide catalyst was hydrogenated overnight on a Parr low pressure apparatus.

The hydrogenation was begun at 48 lb. p.s.i. and fell to a constant pressure of 42 lb. p.s.i. The catalyst was removed by gravity filtration. Removal of the ethyl acetate in vacuo afforded a white solid. Recrystallization from chloroform-methanol gave 9.3 g. of white needles, m.p. 140-142° [lit. (61), m.p. 142°].

Cholestan-3-one I-96. In a 5-l. three-necked flask, equipped with stirrer and dropping funnel, was placed 84.0 g. (0.320 mole) of sodium dichromate, 260 ml. of distilled water, 108 ml. of concentrated sulfuric acid, and 60 ml. of glacial acetic acid. This mixture was cooled to 0° in an ice bath. Cholestanol (65.0 g., 0.170 mole) was dissolved in ca. 1.5 l. of benzene and added dropwise to the rapidly stirred oxidizing solution. After the cholestanol had been added, the stirring was continued for seven hours. The mixture was placed in a separatory funnel and the oxidizing solution

was separated. The benzene layer was washed with 5% sodium bicarbonate solution and water, and dried over magnesium sulfate. Removal of the benzene in vacuo gave a white solid. Recrystallization of this material from chloroform-methanol afforded 60.0 g. of white needles, m.p. 127-129° [lit. (123) m.p. 128-129°].

2α-Bromo-Cholestan-3-one I-97. Cholestanone (55.0 g., 0.140 mole) was dissolved in 2800 ml. of glacial acetic acid. After the solution was cooled to ca. 10° in a cold water bath, 135 ml. of a 1.05 M solution of bromine in glacial acetic acid was added. The orange coloration disappeared after ten minutes and a white precipitate formed. After the solution had stood for one and one-half hours, the mixture was poured into water and extracted with chloroform. The chloroform layers were washed with 5% sodium bicarbonate and water and dried over magnesium sulfate. Removal of the chloroform in vacuo afforded a white residue. Recrystallization of this material from glacial acetic acid provided 46.0 g. of white needles, m.p. 163-166° [lit. (12), m.p. 169-170°].

1-Cholesten-3-one I-98. To 30 ml. of boiling dimethyl acetamide was added 2.0 g. (0.020 mole) of calcium carbonate followed by 3.0 g. (0.007 mole) of 2α-bromo-cholestane-3-one. The solution was heated under reflux for fourteen minutes. The cooled solution was added to 250 ml. of water and extracted with methylene

chloride. The organic layers were washed with 5% hydrochloric acid, water, and dried over magnesium sulfate. Removal of the methylene chloride in vacuo yielded 1.9 g. of oil. Recrystallization from methanol gave 1.6 g. of white plates, m.p. 98-100° [lit. (58) m.p. 98°].

The ultraviolet spectrum exhibits a maximum at 230 mμ, ϵ = 14,500. The infrared spectrum shows a sharp band at 1680 cm^{-1} attributable to both the double band and the carbonyl grouping. The NMR spectrum shows an AB quartet centered at 6.52δ and sharp bands at 62 c.p.s. (19-Me) and 41 c.p.s. (18-Me).

1,2α-Oxido-cholestan-3-one I-99. 1-Cholestene-3-one (10.0 g., 0.025 mole), 100 ml. of 30% hydrogen peroxide and forty drops of 40% sodium hydroxide were added to 250 ml. of ethanol and heated under reflux for fifteen minutes. The solution was poured into ca. 1.3 l. of water and extracted with ether. The organic layers were washed with 5% hydrochloric acid and water and dried over magnesium sulfate. Removal of the solvent in vacuo afforded 9.9 g. of clear oil. Recrystallization from acetone gave 9.0 g. of white solid, m.p. 116-122° [lit. (38), m.p. 122-125°].

2-Cholesten-1α-1-ol I-100. 1,2α-epoxycholestane-3-one (9.0 g., 0.022 mole) was dissolved in 120 ml. of 100% hydrazine hydrate and heated under reflux for fifteen minutes. The hydrazine

solution was poured into water and extracted with ether. The com-
bined organic layers were washed with 10% hydrochloric acid and
water and dried over magnesium sulfate. Removal of the solvent
in vacuo provided 7.2 g. of brown oil. This oil could not be readily
purified through column chromatography or by recrystallization and
was therefore directly incorporated in the next reaction of the
synthetic sequence.

The infrared spectrum shows significant bands at 3400 cm^{-1}
and 1660 cm^{-1}.

2-Cholesten-1-one I-101. 2-Cholestene-1α-1-ol (6.2 g.,
0.016 mole) was dissolved in acetone freshly distilled from potassium
pemanganate. The acetone solution was immersed in an ice bath
and rapidly stirred while 4.3 ml. of Jones reagent was added. After
fifteen minutes the solution was poured into water and extracted with
ether. The organic layers were washed with 5% sodium bicarbonate
solution and water and dried over magnesium sulfate. Removal of
the ether in vacuo afforded 5.8 g. of a brown oil. Chromatography
of this material gave 2.8 g. of clear oil (2:1 hexane-benzene).
Crystallization from methanol gave 2.2 g. of white plates, m.p. 58-
59° [lit. 38, m.p. 59°].

The ultraviolet spectrum shows a maximum 227 mμ,
ϵ = 6,700 (methanol).

Cholestan-1-one I-102. A solution of 1.2 g. (3.0 mmoles) of

2-cholestene-1-one, 70 ml. of cyclohexane and 150 mg. of 5% Pd/C

catalyst was rapidly stirred while being allowed to react with hydrogen

over a twelve hour period. The catalyst was removed by filtration

and the solvent was removed in vacuo. The initial product was

recrystallized from methanol to give 0.96 g. of white needles, m.p.

85-87° [lit. (38), m.p. 85.5°].

The infrared spectrum shows a significant band at 1700 cm^{-1}.

4-Cholesten-3-one p-Toluenesulfonylhydrazone 57. A mixture

of 4-cholestenone, 13.5 g. (0.035 mole), p-toluenesulfonylhydrazine,

7.0 g. (0.037 mole), and 700 ml. of methanol was heated under reflux

for ten minutes. The tosylhydrazone precipitated while the solution

was allowed to stand at room temperature overnight. The white

solid was collected by filtration and then recrystallized from

methanol giving 14.7 g. of needles, m.p. 140-142° [lit. (16) m.p.

142°].

The ultraviolet spectrum displays maxima at 262 mμ,

ε = 14,900, and 226 mμ, ε = 12,500. The infrared spectrum shows

significant bands at 3200 cm^{-1}, 1340 cm^{-1} and 1160 cm^{-1}.

Pyrolysis of 4-Cholestene-3-one p-Toluenesulfonylhydrazone

57 with Sodium Methoxide in Benzene. 4-Cholestene-3-one tosyl-

hydrazone 57, 2.0 g. (0.0036 mole), and 15.32 ml. of 0.47 N sodium

methoxide (0.0072 mole) were employed in the usual manner to form

the sodium salt of the tosylhydrazone.

The pre-formed salt was added to 200 ml. of anhydrous benzene

and then pyrolyzed for 15 hours at an oil bath temperature of 110°.

The crude product was worked-up in the usual manner and afforded

1.32 g. of light yellow oil. Thin layer chromatography indicated two

non-polar products (R_f 0.80, 0.63; hexane) and five polar components,

of which two were predominant (R_f 0.70, 0.60; benzene-ethyl acetate,

19:1). The crude oil was chromatographed on 26 g. of silica gel.

Elution with hexane (fractions 3 through 6) gave 0.48 g. (42%) of

2,4-cholestadiene 109. Two low temperature crystallizations from

ether provided 0.40 g. of white solid, m.p. 66-68°, a]$_D$ +166°

[lit. (119) m.p. 68.5° a]$_D$ +168°].

The infrared spectrum shows a strong band at 679 cm^{-1}

indicative of a steroid 2,4-diene. The ultraviolet spectrum shows

maxima at 266 mμ, ϵ = 5100 and 247 mμ, ϵ = 4,900 (hexane). Its

NMR spectrum displays a multiplet at 5.58 δ attributable to olefinic

protons and sharp bands at 55 c.p.s. (19-, 26- and 27-Me), 50 c.p.s.

(26- and 27-Me), and 42 c.p.s. (18-Me).

Further elution with hexane (fractions 8 through 12) provided

0.49 g. (42%) of spiro(cycloheptatriene 7', 3-cholest-4-ene) 116.

Recrystallization from methanol-chloroform gave 0.40 g. white plates,

m.p. 78.5-80°, a]$_D$ +116°.

<u>Anal</u>. Calcd. for $C_{33}H_{50}$: C, 88.70; H, 11.28.

Found: C, 88.59; H, 11.44

The infrared spectrum shows strong bands at 745 cm^{-1},

709 cm^{-1}, 689 cm^{-1} and 678 cm^{-1}. Its ultraviolet spectrum exhibits

a maximum at 269 mμ, ϵ = 3,100. The NMR spectrum displays

broad bands at 6.37δ (2H) and 6.05δ (2H), and sharp bands at 5.12δ

(1H), 4.98δ (1H) and 4.72δ (1H). Bands due to angular methyl groups

are observed at 60 c.p.s. (19-Me), 56 c.p.s. and 50 c.p.s. (26-

and 27-Me), and 41 c.p.s. (18-Me).

A third component, 0.11 g. (9%) was identified as 4-cholesten-

3a-ol-3-methyl ether <u>117</u> (fractions 21 through 26; hexane-benzene,

3:1). A low temperature crystallization from ether-methanol gave

0.08 g. of white plates, m.p. 44.5-45.5°, a] $_D$ +106°.

<u>Anal</u>. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07

Found: C, 84.01; H, 11.97

The infrared spectrum shows significant bands at 1654 cm^{-1},

1200 cm^{-1}, and 1088 cm^{-1}. The NMR spectrum displays a broad

doublet at 5.38δ (1H), a broad band at 3.45δ (1H) due to the 3β-proton,

and sharp bands at 3.22δ (-OMe), 58 c.p.s. (19-Me), 56 c.p.s. and

50 c.p.s. (26- and 27-Me) and 41 c.p.s. (18-Me).

Elution with 2:1 hexane-benzene (fractions 29 through 34)

afforded 0.03 g. (2%) of 4-cholesten-3β-ol-3-methyl ether <u>118</u>.

This compound was recrystallized from methanol-chloroform as white

needles, 0.02 g., m.p. 74.5-75.5° [lit. (98), m.p. 75-76°].

The infrared spectrum shows bands at 1652 cm^{-1}, 1190 cm^{-1}

and 1090 cm^{-1}. The NMR spectrum displays a broadened singlet

at 5.25δ (1H), a broad band at 3.61δ due to the 3α-proton, a sharp

band at 3.25δ (-OMe) and sharp bands at 63 c.p.s. (19-Me), 55.5

c.p.s. and 49.5 c.p.s. (26- and 27-Me), and 41 c.p.s. (18-Me).

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone <u>57</u>

<u>with Varying Amounts of Sodium Methoxide in Benzene.</u> The pyrolysis

of 2.0 g. (0.0036 mole) of 4-cholestenone tosylhydrazone in 200 ml.

of benzene was carried out with the relative amount of sodium

methoxide being varied from 0.5 equivalents through 10.0 equivalents.

Each reaction was heated for 15 hours under a nitrogen atmosphere

at an oil bath temperature of 110°. The crude product of each reac-

tion was isolated in the usual manner. Chromatography on 20 g. of

silica gel afforded a non-polar fraction (200 ml. of hexane) and a polar

fraction (200 ml. of ether). A thin layer chromatogram and NMR

spectrum was taken of each fraction. These analytical methods

indicated that reactions which employed one equivalent or more

of sodium methoxide gave 2,4-cholestadiene <u>109</u> and spiro(cyclo-

heptatriene-7', 3-cholest-4-ene) <u>116</u> as the non-polar components,

and 4-cholesten-3α-ol-3-methyl ether <u>117</u> and 4-cholestesten-3β-ol-

3-methyl ether <u>118</u> as the major polar components. The relative

yields of <u>109</u> and <u>116</u>, as well as the relative yields of <u>117</u> and <u>118</u>,

were determined from integration of the representative bands in the NMR spectra. Reactions utilizing less than one equivalent of sodium methoxide gave, in addition to 109 and 116, a third non-polar component (R_f 0.76; hexane) and five polar components (benzene-ethyl acetate, 19:1) of which none corresponded to 117 or 118. These products remained unidentified though the additional non-polar component appeared to be a dimer, m.p. 280-300° (dec.).

The ultraviolet spectrum of the dimer shows maxima at 308 mμ, ϵ = 10,600, 295 mμ ϵ = 15,500, and 284 mμ, ϵ = 12,400. Thin layer chromatography shows this compound to have the same retention time as that of dimer 127 (R_f 0.50, hexane). The results of each reaction are summarized in Table 26.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57 with Sodium Methoxide in Varying Amounts of Benzene. The pyrolysis of 1.0 g. (0.0018 mole) of 4-cholestenone tosylhydrazone was carried out with 7.66 ml. of 0.47 N sodium methoxide (0.0036 mole) and various amounts of benzene ranging from 25 ml. to 500 ml. The crude product of each reaction was isolated in the usual way. Chromatography on 12 g. of silica gel afforded a non-polar fraction (120 ml. of hexane) and a polar fraction (120 ml. of ether). Thin layer chromatography of each fraction indicated 109 and 116 as the non-polar constituents while 117 and 118 were the major polar components. The results of these experiments are summarized in

Table 26. NaOMe Treatment of 4-Cholestenone Tosylhydrazone 57.

Equivalents of NaOMe	Crude Yield	Non-Polars	109:116	Polars	117:118
10	1.5582 g.	60%	0.9	40%	4.0
5	1.4808 g.	71%	1.1	29%	---
2	1.3209 g.	84%	1.0	16%	3.9
1	1.5257 g.	87%	1.0	13%	---
0.75	1.6409 g.	45.%	1.1	*55%	none
0.50	1.7166 g.	37%	1.1	*63%	none

*yields are corrected so as not to include the unreacted tosylhydrazone.

Table 27.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57

with Sodium Hydride in Benzene. To a mixture of 2.00 g. (0.0036

mole) of 4-cholestenone tosylhydrazone and 200 ml. of anhydrous

benzene was added 0.43 g. (0.018 mole) of sodium hydride. This

solution was heated for fifteen hours at an oil bath temperature of

110°. The sodium hydride was removed from the cooled solution

through gravity filtration. The organic layer was worked-up in the

usual manner to give 1.63 g. of a yellow oil. Thin layer chromatog-

raphy indicated two non-polar products (R$_f$ 0.82, 0.64; hexane) and

six polar components. The crude oil was chromatographed on 25 g.

of silica gel. Elution with hexane gave 0.46 g. (29%) of 2,4-

cholestadiene 109 and 0.42 g. (27%) of spiro(cycloheptatriene-7', 3-

cholest-4-ene 116.

The remaining material on the column was removed with ether

to afford 0.73 g. of yellow oil. Thin layer chromatography showed a

mixture of six components, the major component being the starting

tosylhydrazone.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57

with Varying Amounts of Sodium Hydride in Benzene. The pyrolysis

of 2.0 g. (0.0036 mole) of 4-cholestenone tosylhydrazone in 200 ml.

of benzene was carried out with the relative amount of sodium hydride

Table 27. Effect of Changing Sodium Salt 106 Concentration.

Equivalents of NaOMe	g. 57/ml. of benzene	Molarity	Non-Polars	Polars
2	1/25	0.144	50%	50%
2	1/50	0.072	78%	22%
2	1/100	0.036	84%	16%
2	1/500	0.007	89%	11%

being varied between 10 equivalents and 0.5 equivalents. Each

reaction was heated at an oil bath temperature of 110° for 15 hours.

After removal of the sodium hydride, the reactions were worked-up

in the usual way. Chromatography on 20 g. of silica gel afforded a

non-polar fraction (200 ml. of hexane) and a polar fraction (200 ml.

of ether). A thin layer chromatogram was taken of each fraction and

an NMR spectrum was taken of each non-polar fraction. These

methods indicated that the non-polar components were 2,4-cholestadiene

109 and spiro(cycloheptatriene-7', 3-cholest-4-ene) 116, and the polar

fraction was a complex mixture containing a large amount of starting

tosylhydrazone. The relative yields of 109 to 116 were determined

from integration of the representative bands in the NMR spectra.

The results of these experiments are summarized in Table 28.

Alumina-catalyzed Aromatization of Spiro(cycloheptatriene-

7', 3-cholest-4-ene)116. A hexane solution of Spiro(cycloheptatriene-

7', 3-cholest-4-ene) 116, 0.15 g., was added to 10 g. of neutral

alumina. Compound 116 was allowed to remain on the column for

4 hours. Elution with 50 ml. of hexane-benzene, 5:1, provided

0.14 g. of an oil identified as a mixture 121 of 3α-phenyl-cholest-4-

ene and 3β-phenyl-cholest-4-ene. All attempts at crystallization

failed. Thin layer chromatography of the oil gave one band (R_f 0.63;

hexane). The NMR spectrum shows a band at 7.22δ due to five

aromatic protons, a broad band at 5.75δ equivalent to one olefinic

Table 28. NaH Treatment of Tosylhydrazone 57.

Equivalents of NaH	Crude Yield	Non-Polars	109:116	Polars
10	1.6484 g.	53%	1.0	47%
5	1.6312 g.	54%	1.1	46%
2	1.6233 g.	52%	1.0	48%
1	1.6000 g.	37%	1.0	63%

proton, and sharp bands at 61 c. p. s. (19-Me) and 40 c. p. s. (18-Me).

The ultraviolet spectrum exhibits no maximum above 210 mμ.

The oily mixture 121 was added as a hexane solution to a

column of 10 g. of basic alumina. After 2 hours, elution with 50 ml.

of 5:1 hexane-benzene gave 0. 12 g. of white crystalline material

identified as 3-phenyl-cholest-2-ene 122. Two recrystallizations

from acetone gave 0. 08 g. of white needles, m. p. 133-136°, $\alpha]_D$

+58° [lit. (131), m. p. 126-127°, $\alpha]_D$ + 53°] .

Anal. Calcd. for $C_{33}H_{50}$: C, 88. 70; H, 11. 28

Found: C, 88. 62; H, 11. 38

The infrared spectrum displays a weak band at 3020 cm^{-1} and

strong bands at 748 cm^{-1} and 690 cm^{-1}. The infrared spectrum of

122 was identical with the infrared spectrum of an authentic sample

of 3-phenyl-cholest-2-ene 124. The ultraviolet spectrum shows a

maximum at 248 mμ, ϵ = 13, 600. The NMR spectrum shows a band

at 7. 25δ, a broad band at 6. 02δ due to an olefinic proton, and sharp

bands at 56. 5 c. p. s. and 50 c. p. s. (26- and 27-Me), 48 c. p. s. (19-

Me), and 40. 5 c. p. s. (18-Me).

Spiro(cycloheptatriene-7', 3-cholest-4-ene) 116 was allowed to

stand for 4 hours on acid-washed alumina. Elution with 5:1 hexane-

benzene gave an oil. Thin layer chromatography showed one band

$(R_f$ 0. 64; hexane).

The NMR spectrum of this oil shows it to be 77% starting

material 116 and 23% of an aromatic component, presumably either 121 or 122.

3-Phenylcholestan-3α-ol and 3-Phenylcholestan-3β-ol 123.

Bromobenzene, 0.5 g. (0.0032 mole) in 10 ml. of tetrahydrofuran was added dropwise from an addition funnel to 50 ml. of anhydrous tetra-hydrofuran containing 0.5 g. (0.021 mole) of magnesium turnings. The resulting solution was refluxed for 1 hour. The solution was allowed to cool and 1.1 g. (0.0028 mole) of cholestan-3-one dissolved in 25 ml. of tetrahydrofuran was added. This mixture was then refluxed for 8 hours. The cooled solution was poured onto a saturated ammonium chloride solution and extracted with ether. The combined organic layers were dried over magnesium sulfate. Removal of the solvent in vacuo afforded 1.20 g. of a light yellow oil which slowly crystallized. This oily solid was designated as a mixture 123 of 3-phenylcholestan-3α-ol and 3-phenylcholestan-3β-ol. The mixture was not purified further and was used directly in the next reaction of the synthetic sequence.

The infrared spectrum shows a broad band at 3400 cm^{-1} and strong bands at 690 cm^{-1} and 752 cm^{-1}.

3-Phenylcholest-2-ene 124. A mixture of 1.2 g. (0.0026 mole) of 3-phenylcholestan-3-ol (α and β isomers), 12 ml. of pyridine and 1.6 ml. of thionyl chloride was maintained at ice bath temperature for 3 minutes. The reaction mixture was poured into water and

extracted with chloroform. The crude product was isolated in the

usual manner to give 1.20 g. of brown oil. Column chromatography

of this material on 30 g. of silica gel gave 0.76 g. of crystals

(fraction 1; benzene). Recrystallization from acetone gave 0.74 g.

of long needles, m.p. 137-138°, a]$_D$ +65° [lit. 131, m.p. 126-127°;

lit. 128 anisotropic liquid 132° and m.p. 144°].

The infrared spectrum displays a weak band at 3020 cm^{-1} and

strong bands at 748 cm^{-1} and 690 cm^{-1}. The ultraviolet spectrum

shows an absorption maximum at 248 mμ, ϵ = 13,300. The NMR

spectrum displays a band at 7.25δ, a broad band at 6.02δ, and sharp

bands at 56 c.p.s. and 50 c.p.s. (26- and 27-Me), 48 c.p.s. (19-

Me), and 40.5 c.p.s. (18-Me).

Alumina-catalyzed Reaction of Cholest-4-en-3a-ol-3-methyl

ether 117. Cholest-4-en-3a-ol-3-methyl ether 0.11 g., was added

as a hexane solution to a column of 10 g. of neutral alumina. This

mixture was allowed to stand for 1 hour. Elution with 50 ml. of

hexane afforded 0.084 g. (81%) of white crystals identified as 3,5-

cholestadiene 112. Recrystallization from acetone provided needles,

m.p. 79-80° [lit. (42), m.p. 80°]. Thin layer chromatography

of 112 and an authentic sample of 3,5-cholestadiene showed they

possessed identical R$_f$ values (R$_f$ 0.85; hexane).

The ultraviolet spectrum shows a maximum at 235 mμ,

ϵ = 18,500.

Elution with benzene gave 0.007 g. (7%) of an oil which was discarded. Further elution with 50 ml. of ether afforded 0.012 g. (12%) of white solid. Thin layer chromatography indicated this material was a mixture of 4-cholesten-3α-ol 113 and 4-cholesten-3β-ol 114 (R_f 0.24, 0.15; benzene-ethylacetate, 1:1). The α-isomer was the major product but no attempt was made to determine the relative amounts of the two isomers.

The infrared spectrum shows the same bands as does the infrared spectrum of an authentic sample of a mixture of the epimeric alcohols.

Alumina-catalyzed Reaction of Cholest-4-en-3β-ol-3-methyl ether 118. A hexane solution of 0.14 g. of cholest-4-en-3β-ol-3 methyl ether 118 was added to a column of 10 g. of neutral alumina. The methyl ether 118 was allowed to stand on the column for 4 hours. Elution with 50 ml. of hexane afforded 0.084 g. (70%) of white crystals identified as 3,5-cholestadiene 112. Recrystallization from acetone gave long needles, m.p. 78-80° [lit. 42, m.p. 80°]. Thin layer chromatography of this material and an authentic sample of 3,5-cholestadiene showed they possessed identical R_f values (R_f 0.85; hexane).

The ultraviolet spectrum shows a maximum at 235 mμ, ϵ = 16,500.

Elution with 50 ml. of benzene gave 0.013 g. (10%) of an oil which was discarded. Further elution with 50 ml. of ether gave 0.024 g. (20%) of a white solid identified as a mixture of 4-cholesten-3α-ol 113 and 4-cholesten-3β-ol 114. The assignment of structures was verified by comparative thin layer chromatography (R_f 0.24, 0.16; 1:1 benzene-ethylacetate). The α-isomer was the major component but no attempt was made to determine the relative amounts of the two isomers.

The infrared spectrum shows the same bands as does the infrared spectrum of an authentic sample of a mixture of the spimeric alcohols.

Cholest-4-en-3α-ol 113 and Cholest-4-en-3β-ol 114. A mixture of 4-cholesten-3-one, 0.50 g. (0.0013 mole), 50 ml. of anhydrous ether and 0.05 g. (0.0013 mole) of lithiumaluminumhydride was heated under reflux overnight. The excess hydride was destroyed with methanol and the mixture was poured into a concentrated solution of sodium potassium tartrate. The organic layer was dried over magnesium sulfate and the ether was then removed in vacuo providing 0.48 g. of a white solid. Thin layer chromatography indicated two bands (R_f 0.24, 0.15; benzene-ethyl acetate, 1:1).

The infrared spectrum shows a broad band at 3450 cm^{-1} (-OH stretch), a weak band at 1640 cm^{-1} (c = c stretch), and strong bands at 1210 cm^{-1} and 1015 cm^{-1}.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57

with Sodium Methoxide in Diglyme. To 3.0 g. (0.0054 mole) of 4-

cholestenone tosylhydrazone was added 23 ml. of 0.47 N sodium

methoxide (0.0108 mole). This mixture was used in the usual way to

form the sodium salt of the tosylhydrazone. Anhydrous diglyme (400

ml.) was distilled onto the sodium salt. The resulting solution was

heated at an oil bath temperature of 120°. At the end of 4 hours, the

sodium p-toluenesulfonate precipitate was removed by gravity filtra-

tion and the diglyme was removed in vacuo. The residual oil was

dissolved in hexane and washed ten times with 50 ml. portions of

water. The hexane solution was dried over magnesium sulfate.

Removal of the solvent in vacuo afforded 2.16 g. of a yellow oil.

Thin layer chromatography indicated one significant non-polar

product (R_f 0.79; hexane) and four polar components (R_f 0.61, 0.54,

0.44, 0.22; benzene-ethyl acetate, 19:1).

The crude oil was chromatographed on 40 g. of silica gel.

Elution with 500 ml. of hexane (fraction 1) gave 0.755 g. (35%) of a

component whose properties were identical to those of 2,4-

cholestadiene 109.

Further elution with 300 ml. of 2:1 hexane-benzene (fraction 3)

gave 0.210 g. (10%) of an oil. This component was identical with 117

which was designated as 4-cholesten-3a-ol-3-methyl ether.

A third compound, 0.140 g. (6%), was eluted with 300 ml. of

1:1 hexane-benzene (fraction 4). This crystalline material showed properties identical with those of 4-cholesten-3β-ol-3-methyl ether 118.

Elution with benzene-ether, 20:1, (Fractions 5 and 6) gave 0.205 g. (8%) of an oil which was shown to be 4-cholesten-3α-p-tolysulfone 125 by comparison of its properties with 125 isolated from pyrolysis of 57 in cyclohexene.

Continued elution with benzene-ether, 20:1, (fractions 8 through 10) gave 0.854 g. (40%) of an oil. This oil 124 was a complex mixture of isomers resulting from insertion of the steroidal carbene into the various carbon-hydrogen bonds of diglyme. Thin layer chromatography showed one clear band (R_f 0.20; benzene-ethyl acetate; 19:1).

The infrared spectrum shows a weak band at 1660 cm^{-1} and a strong band at 1100 cm^{-1}. The NMR spectrum displays a broad band at 5.20δ (1H), a broadened singlet at 3.50δ, a sharp band at 3.2δ (Combined bands 14 H) and sharp bands at 59.5 c.p.s. (19-Me), 55.5 c.p.s. and 49.5 c.p.s. (26- and 27-Me), and 41 c.p.s. (18-Me).

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57 with Sodium Methoxide in Heptane. 4-Cholesten-3-one tosylhydrazone, 1.0 g. (0.0018 mole), and 7.66 ml. of 0.47 N sodium methoxide (0.0036 mole) were employed in the usual manner to form the sodium salt of the tosylhydrazone.

To the pre-formed salt was added 100 ml. of dry heptane. The resulting solution was pyrolyzed for 15 hours at an oil bath temperature of 105°. The reaction was worked-up in the usual manner affording 0.701 g. of a colorless oil. Thin layer chromatography showed the presence of two non-polar products (F_f 0.88, 0.81; hexane) and four polar components (R_f 0.40, 0.29, 0.17, 0.10; benzene-ethyl acetate, 19:1). The crude oil was chromatographed on 15 g. of silica gel. Elution with 100 ml. of hexane gave 0.542 g. (90%) of a clear oil. Thin layer chromatography showed two bands (R_f 0.89, 0.81; hexane). The NMR spectrum of this oil shows a multiplet at 5.63δ (relative area = 85) characteristic of a 2,4-diene, and a broadened singlet at 5.13δ (relative area = 40) attributable to the C-4 proton of products arising from insertion of the steroidal carbene into C-H bonds of heptane. The integration indicates a mixture consisting of 1.4 parts of insertion products 126 and 1.0 parts of 2,4-cholestadiene 109.

The remaining material on the column was removed with ether affording 0.062 g. (10%) of light yellow oil. Thin layer chromatography of this oil indicated the presence of 4-cholesten-3α-ol-3-methyl ether 117, 4-cholesten-3β-ol-methyl ether 118, and 4-cholesten-3α-p-tolysulfone 125.

The non-polar oil was then chromatographed on 12 g. of silica gel impregnated with silver nitrate. Elution with hexane

(fractions 3 through 7) afforded 0.307 g. (51%) of a clear oil

designated as a mixture of isomers of 3-heptyl-cholest-4-ene 126.

Thin layer chromatography showed only one band (R_f 0.88, hexane),

yet this oil resisted all attempts at crystallization.

The ultraviolet spectrum shows no absorption above 220 mμ.

The infrared spectrum shows a medium band at 676 cm^{-1}. The NMR

spectrum displays a broad band at 5.13δ (1H against 65 H for the

methyl and methylene mass), and sharp bands at 58.5 c.p.s. (19-Me),

55 c.p.s. and 49.5 c.p.s. (26- and 27-Me), and 41 c.p.s. (18-Me).

Further elution with 6:1 benzene-ethyl acetate (fractions 14

through 17) gave 0.217 g. (36%) of a clear oil. This material was

identified as 2,4-cholestadiene through comparison of its physical

properties with those of 109.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57

with Sodium Methoxide in Celite. To 4-cholesten-3-one tosylhydrazone,

4.50 g. (0.0081 mole), dissolved in 200 ml. of anhydrous methanol

was added 33.8 ml. of 0.46 N sodium methoxide (0.0162 mole). The

solvent was removed in vacuo and the residual salt was further dried

overnight at 0.05 mm. The salt was ground in a mortar and pestle

and then mixed thoroughly with 5.5 g. of celite. This mixture was

heated at 110° until nitrogen evolution had ceased. The celite mix-

ture was poured into hot hexane and, after stirring for ca. 1/2 hour,

the celite was removed by vacuum filtration. The hexane layer was

worked-up in the usual manner to give 2.87 g. of a yellow oil. Thin layer chromatography indicated the presence of three non-polar components (R_f 0.84, 0.79, 0.74; hexane) and three polar components (R_f 0.66, 0.59, 0.48; benzene-ethyl acetate, 19:1). Column chromatography on 50 g. of silica gel gave, on elution with hexane (fractions 1 and 2), 0.055 g. (2%) of an oil which was discarded. Further elution with hexane (fractions 3 through 5) gave 0.778 g. (30%) of 2,4-cholestadiene identified by comparison of its physical properties with those of 109. Continued elution with hexane (fractions 6 through 12) afforded 0.331 g. (12%) of a white solid. Recrystallization from methanol gave a white powder m.p. 227-237° (dec.) which is tentatively identified as an isomeric mixture of dimers 127.

The ultraviolet spectrum shows maxima at 284 mμ, ϵ = 12,700, 295 mμ, ϵ = 15,800 and 308 mμ, ϵ = 10,800.

Elution with 200 ml. of ether (fraction 13) afforded 1.488 g. (66%) of a yellow oil. Thin layer chromatography showed this material was a mixture of the 3α- and 3β-methyl ethers, 117 and 118, and the 3α-sulfone 125.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57 with Sodium Methoxide in Carbon Tetrachloride. A mixture of 4-cholestenone tosylhydrazone, 5.00 g. (0.009 mole), and 39 ml. of 0.46 N sodium methoxide, (0.018 mole), was employed in the usual manner to form the sodium salt of the tosylhydrazone.

Carbon tetrachloride, 650 ml., was added to the pre-formed salt. The resulting solution was heated under reflux for 15 hours. The cooled solution was worked-up in the usual manner and provided 4.161 g. of a dark red oil. Thin layer chromatography showed the presence of at least five non-polar components of which one was very predominant (R_f 0.72; hexane). In addition, thin layer chromatography (benzene-hexane, 4:1) of a concentrated sample showed the presence of eight polar components. The red oil was chromatographed on 50 g. of silica gel and gave, on elution with hexane (fractions 2 through 4) 1.102 g. (28%) of a colorless oil identified as 3-(1',1'-dichloro-ethylidene)-cholest-4-ene (129). Low temperature recrystallization from ether-methanol afforded 0.714 g. of small needles, m.p. 71.5 - 73°, $\alpha]_D$ +121°.

Anal. Calcd. for $C_{28}H_{44}Cl_2$: C, 75.01; H, 9.89; Cl, 15.01

Found: C, 74.85; H, 9.94; Cl, 14.96

The infrared spectrum shows a weak band at 1620 cm^{-1}, strong bands at 915 cm^{-1} and 862 cm^{-1}, and a medium band at 806 cm^{-1}. The ultraviolet spectrum displays a maximum at 260 mμ, ϵ = 21,000. The NMR spectrum exhibits a sharp band at 6.07δ attributable to an olefinic proton and sharp bands at 63.0 c.p.s. (19-Me), 55.5 c.p.s. (26,27-Me), 49.0 c.p.s. (26,27-Me) and 41.5 c.p.s. (18-Me).

Further elution with hexane (fractions 5 through 13) gave a 0.506 g. (13%) of clear oil. Thin layer chromatography indicated the

oil contained five components. No attempt was made to purify this fraction. Elution with hexane-benzene, 6:1, (fractions 14 through 23) provided 0.405 g. (10%) of a red oil. Thin layer chromatography showed this oil was a mixture of at least four components. Continued elution with benzene gave 0.427 g. (11%) of a red-brown oil. This oil was shown by thin layer chromatography to contain at least five compounds. Elution with ether provided 1.548 g. (38%) of a dark brown oil. Thin layer chromatography indicated the presence of at least four components including the starting tosylhydrazone.

The thin layer chromatography studies of these polar fractions verified the complete absence of 4-cholesten-3α-ol-3-methyl ether 117, 4-cholesten-3β-ol-3-methyl ether 118, and 4-cholesten-3α-ol-3-p-tolyl sulfone 125.

Pyrolysis of 4-Cholesten-3-one Tosylhydrazone 57 with Sodium Hydride in Carbon Tetrachloride. A mixture of 4-cholesten-3-one tosylhydrazone 3.00 g. (0.0054 mole), 0.60 g. (0.026 mole) of sodium hydride and 300 ml. of carbon tetrachloride was heated under reflux for 15 hours. Removal of the sodium hydride by gravity filtration followed by work up of the filtrate in the usual manner afforded 2.46 g. of red-brown oil. Thin layer chromatography showed one predominant non-polar product (R_f 0.74; hexane). The red oil was chromatographed on 40 g. of silica gel. Elution with hexane (fractions 3 and 4) gave 0.56 g. (23%) of clear oil. Low temperature recrystallization from

ether-methanol gave compact needles, m.p. 72-74°. This material

showed properties identical with those of 3-(1',1'-dichloroethylidene)-

cholest-4-ene 129.

Pyrolysis of Cholest-4-en-3-one p-Toluenesulfonylhydrazone 57

with Sodium Methoxide in Cyclohexene. A mixture of 4-cholestenone

tosylhydrazone, 5.10 g. (0.0092 mole), and 40 ml. of 0.46 N sodium

methoxide, (0.0184 mole) was utilized in the usual way to form the

sodium salt of the tosylhydrazone.

Cyclohexene, 650 ml., was added to the sodium salt. This

solution was heated under reflux for 15 hours. Isolation of the reac-

tion products in the usual way afforded 4.64 g. of a light yellow oil.

Thin layer chromatography (hexane) indicated at least three non-polar

products (R_f 0.67, 0.60, 0.56) and three more polar products (R_f

0.56, 0.37, 0.26; benzene). Column chromatography of this mixture

on 60 g. of silica gel gave, on elution with hexane, 3.53 g. of a clear

oil. Thin layer chromatography on silica gel impregnated with silver

nitrate showed this oil was a mixture of at least three components

(R_f 0.67, 0.51, 0.22; hexane-benzene, 9.5:1). The hexane fraction

was set aside for further chromatography on silica gel impregnated

with silver nitrate.

Further elution (fractions 4 through 8; hexane-benzene, 2.5:1)

afforded 0.12 g. (3%) of a clear oil identified as cholest-4-en-3α-ol-

3-methyl ether by comparison of its physical properties with those

of **117**.

A second polar component (fractions 9 through 13; hexane-benzene, 1:1) afforded 0.084 g. (2%) of cholest-4-en-3β-ol-3-methyl ether identified by comparison of its physical properties with those of **118**.

Continued elution (fractions 14 through 16; benzene) provided 0.650 g. (14%) of an oil identified as cholest-4-ene-3α-p-tolylsulfone **125**. Recrystallization from methanol-ether afforded 0.310 g. of a white powder, m.p. 118-120°, a]$_D$ +95°.

<u>Anal</u>. Calcd. for $C_{34}H_{52}SO_2$: C, 77.81; H, 9.99.

Found: C, 77.91; H, 10.16

The infrared spectrum displays significant bands at 1310 cm^{-1}, 1300 cm^{-1} and 1138 cm^{-1}. The ultraviolet spectrum shows a maximum at 224 mμ, ε = 9,400. The NMR spectrum shows an A_2B_2 quartet centered at 7.50δ (4H), a broadened doublet at 5.30δ (1H), a broad band at 3.43δ (1H), a sharp band at 2.44δ (3H), and sharp bands due to angular methyl groups at 56 c.p.s. (19-, 26- and 27-Me), 49.5 c.p.s. (26- and 27-Me) and 38 c.p.s. (18-Me).

The hexane fraction was rechromatographed on 70 g. of silica gel impregnated with silver nitrate. Elution with hexane (fractions 1 through 13) afforded 0.880 g. (23%) of endo-spiro (4-cholestene-3, 7'-bicyclo[4.1.0] heptane) **132**. Low temperature recrystallization from methanol-ether gave 0.510 g. of white solid, m.p. 80-82°. A

further recrystallization from chloroform-methanol afforded the

analytical sample, 0.077 g., m.p. 81.5-82.5°, $\alpha]_D$ + 137°.

Anal. Calcd. for $C_{33}H_{54}$: C, 87.93; H, 12.07

Found: C, 87.99; H, 12.03

The infrared spectrum shows a weak band at 1024 cm^{-1} and a

strong band at 852 cm^{-1}. The ultraviolet spectrum exhibits a maxi-

mum at 211 mμ, ϵ = 14,600. The NMR spectrum displays a sharp

band at 5.02δ due to an olefinic proton and sharp bands at 55.5 c.p.s.

and 49.5 c.p.s. (26- and 27-Me), at 61.5 c.p.s. (19-Me), and 41.5

c.p.s. (18-Me).

Additional elution (fractions 15 through 20; hexane-benzene,

20:1) afforded 0.918 g. (24%) of exo-spiro(4-cholestene-3,7'-bicyclo

[4.1.0] heptane) 133. Low temperature recrystallization afforded

0.551 g. of white solid, m.p. 88-90°. A further recrystallization of

0.100 g. from methanol-chloroform provided 0.064 g. of needles,

m.p. 90-91°, $\alpha]_D$ +70°.

Anal. Calcd. for $C_{33}H_{54}$: C, 87.93; H, 12.07

Found: C, 87.72; H, 12.34

The infrared spectrum exhibits a weak band at 1020 cm^{-1} and

a strong band at 862 cm^{-1}. The ultraviolet spectrum shows no maxi-

mum above 207 mμ. The NMR spectrum shows a sharp band at 4.37δ

due to an olefinic proton and sharp bands at 55 c.p.s. and 49 c.p.s.

(26- and 27-Me), at 61 c.p.s. (19-Me) and 40.5 c.p.s. (18-Me).

Elution with 6:1 hexane-benzene (fractions 27 through 30) provided 0.194 g. (6%) of a presumably dimeric material. Recrystallization from chloroform-methanol afforded 0.068 g. of white solid, m.p. 211-218°.

The infrared spectrum shows a weak band at 1652 cm^{-1} and medium bands at 858 cm^{-1} and 676 cm^{-1}. The ultraviolet spectrum shows no maximum above 220 mμ. The NMR spectrum shows a broad band at 5.30δ and sharp bands at 59.5 c.p.s. (19-Me) and 41 c.p.s. (18-Me).

A fourth non-polar component, 0.542 g. (14%), was identified as 3α-(2'-cyclohexenyl)-cholest-4-ene **134.** Low temperature recrystallization from methanol-ether afforded 0.284 g. of compact crystals, m.p. 61-62.5°, α]$_D$ + 79°.

Anal. Calcd. for C$_{33}$H$_{54}$: C, 87.93; H, 12.07

Found: C, 87.68; H, 12.01

The infrared spectrum shows weak bands at 3020 cm^{-1} and 1648 cm^{-1}, and medium bands at 858 cm^{-1} and 720 cm^{-1}. The ultraviolet spectrum shows no maximum above 220 mμ. The NMR spectrum exhibits a sharp band at 5.62δ (2H) and a broad band at 5.21δ (1H), both attributable to olefinic protons, and sharp bands at 55.5 c.p.s. and 49.5 c.p.s. (26- and 27-Me), at 59 c.p.s. (19-Me) and 41 c.p.s. (18-Me).

Elution with 2:1 hexane-benzene (fractions 39 through 46)

afforded 0. 352 g. (9%) of 3β-(2'-cyclohexenyl)-cholest-4-ene <u>135</u>.

Recrystallization from methanol-chloroform provided 0. 178 g. of

plates, m.p. 109-110°, $\alpha]_D$ +130°.

<u>Anal</u>. Calcd. for $C_{33}H_{54}$: C, 87.93; H, 12.07

Found: C, 87.93; H, 12.07

The infrared spectrum shows weak bands at 3030 cm^{-1} and

1650 cm^{-1}, and medium bands at 860 cm^{-1} and 720 cm^{-1}. The ultra-

violet spectrum shows no maximum above 220 mμ. The NMR

spectrum displays bands at 5. 65δ (2H) and 5. 28δ (1H), attributable

to olefinic protons, and sharp bands at 56 c. p. s. and 50 c. p. s. (26-

and 27-Me), at 59 c. p. s. (19-Me) and 41. 5 c. p. s. (18-Me).

Alumina-catalyzed Rearrangement of endo-Spiro(4-cholestene-

3, 7'-bicyclo[4. 1. 0] heptane) <u>132</u>. A hexane solution of 0. 060 g.

of spiro compound <u>132</u> was added to 2 g. of neutral alumina. Com-

pound <u>132</u> remained on the column for 3. 5 hours and elution with 4:1

hexane-benzene gave 0. 052 g. of a crystalline solid designated as

3-(1'-cyclohexenyl)-cholest-2-ene <u>176</u>. This product was recrystal-

lized from chloroform-methanol as long needles, 0. 039 g. , m. p.

151-152°, $\alpha]_D$ -104°.

<u>Anal</u>. Calcd. for $C_{33}H_{54}$: C, 87.93; H, 12.07

Found: C, 87.95; H, 12.05

The infrared spectrum shows a significant band at 645 cm^{-1}.

The ultraviolet spectrum exhibits maxima at 234 mµ, ϵ = 17,200, 242 mµ, ϵ = 19,600, and 250 mµ, ϵ = 12,700. The NMR spectrum exhibits bands at 5.63δ (1H) and 5.22δ (1H) attributable to olefinic protons and sharp bands at 52 c.p.s. (19-Me), 42 c.p.s. (18-Me), and 56 c.p.s. and 50 c.p.s. (26- and 27-Me).

Alumina-catalyzed Rearrangement of exo-Spiro(4-cholestene-3,7'-bicyclo[4.1.0] heptane) 133. Exo-spiro(4-cholestene-3,7'-bicyclo[4.1.0] heptane) 133, 0.060 g., was added to 2 g. of neutral alumina and allowed to stand for 3.5 hours. Elution with 4:1 hexane-benzene provided 0.049 g. of 3-(1'-cyclohexenyl)-cholest-2-ene 176. Recrystallization of the crude solid from chloroform-methanol gave 0.038 g. of needles, m.p. 149-151°. The infrared spectrum displays a medium band at 645 cm^{-1}. The ultraviolet spectrum displays maxima at 234 mµ, ϵ = 19,400, 242 mµ, ϵ = 20,600, and 250 mµ, ϵ = 14,300. The NMR spectrum shows bands at 5.63δ (1H) 5.22δ (1H) due to olefinic protons, and sharp bands at 52 c.p.s. (19-Me), 42 c.p.s. (18-Me) and 56 c.p.s. and 50 c.p.s. (26- and 27-Me).

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57 with Sodium Methoxide in Tetrachloroethylene. A mixture of 1.0 g. (0.0018 mole) of 4-cholesten-3-one tosylhydrazone and 7.66 ml. of 0.47 N sodium methoxide (0.0036 mole) was utilized in the usual manner to form the sodium salt of the tosylhydrazone. Tetrachloroethylene, 100 ml., was added to the salt. The resulting solution was

heated for 15 hours at an oil bath temperature of 110°. The initial

product was isolated in the usual manner and provided 0.803 g. of a

brown oil. Thin layer chromatography indicated the crude mixture

consisted of one non-polar component (R_f 0.75; hexane) and at least

four polar components (R_f 0.40, 0.29, 0.17, 0.10; benzene-ethyl

acetate, 19:1). Chromatography of the crude mixture on 12 g. of

silica gel gave, on elution with hexane, 0.556 g. (75%) of an oil which

crystallized on standing. This compound was designated as spiro(4-

cholestene-3,1'-tetrachlorocyclopropane) 136. Recrystallization from

acetone afforded 378 mg. of white needles, m.p. 119-120°, a]$_D$ +74°.

Anal. Calcd. for $C_{29}H_{44}Cl_4$: C, 65.40; H, 8.24; Cl, 26.36

Found: C, 65.27; H, 8.28; Cl, 26.59

The infrared spectrum shows a weak band at 1640 cm^{-1} and a

broad doublet centered at 835 cm^{-1}. The ultraviolet spectrum dis-

plays a maximum at 206 mμ, ε = 14,100. The NMR spectrum shows

a broadened singlet at 5.12 δ and sharp bands at 65 c.p.s. (19-Me),

55 c.p.s. (26, 27-Me), 49 c.p.s. (26,27-Me) and 42 c.p.s. (18-Me).

The remaining material was removed from the column with

ether and provided 0.190 g. (25%) of a brown oil. Thin layer

chromatography (benzene-ethyl acetate, 19:1) indicated the presence

of at least five components, of which bands corresponded to 4-

cholesten-3α-ol-methyl ether 117, 4-cholesten-3β-ol-methyl ether

118, and 4-cholesten-3α-p-tolyl-sulfone 125.

Pyrolysis of 4-Cholesten-3-one p-Toluenesulfonylhydrazone 57

with Sodium Hydride in Tetrachloroethylene. A mixture of 2.00 g.

(0.0036 mole) of 4-cholestenone tosylhydrazone, 100 ml. of

tetrachloroethylene and 0.43 g. (0.018 mole) of sodium hydride was

heated under reflux for 4 hours. Removal of the sodium hydride by

gravity filtration followed by work-up of the filtrate in the usual

manner afforded 1.62 g. of a red oil. Thin layer chromatography

showed one non-polar component (R_f 0.77; hexane). Column

chromatography on silica gel gave, on elution with hexane, 0.92 g.

(57%) of a clear oil which slowly crystallized. Recrystallization from

acetone gave 0.67 g. of needles, m.p. 119-120°. This material

showed properties which were consistent with those of spiro(4-

cholestene-3, 1'-tetrachlorocyclopropane) 136.

Alumina-catalyzed Rearrangement of Spiro(4-cholestene-3, 1'-

tetrachlorocyclopropane) 136. Spiro tetrachlorocyclopropyl com-

pound 136, 0.200 g., was added to a column of 10 g. of neutral

alumina and allowed to stand overnight. Elution with 50 ml. of 6:1

hexane-benzene gave 0.157 g. of white solid identified as 3-(tri-

chloroethylene)-cholest-3, 5 diene 177. Recrystallization from

acetone gave 0.127 g. of white needles, m.p. 145-146°, a]$_D$ -131°.

Anal. Calcd. for $C_{29}H_{43}Cl_3$: C, 69.99; H, 8.65; Cl, 21.36

Found: C, 70.16; H, 8.80; Cl, 21.57

The ultraviolet spectrum shows a maximum at 268 mμ,

$\epsilon = 10,700$. The infrared spectrum shows medium bands at 641 cm^{-1}, 676 cm^{-1} and 1635 cm^{-1}, and strong bands at 873 cm^{-1} and 958 cm^{-1}. The NMR spectrum displays a broadened singlet at 6.15δ (1H) and a broad band at 5.56δ (1H), both attributable to vinyl hydrogens, and sharp bands at 57 c.p.s. (19-Me), 55.5 c.p.s. (26, 27-Me) 49.5 c.p.s. (26,27-Me), and 43 c.p.s. (18-Me).

Pyrolysis of 4-Cholestene-3-one p-Toluenesulfonylhydrazone 57 with Sodium Methoxide in an Equimolar Mixture of Tetrachloro-ethylene and Cyclohexane. 4-Cholestenone tosylhydrazone, 2.0 g. (0.0036 mole), and 15.6 ml. of 0.46 N sodium methoxide, (0.0072 mole), were used in the usual manner to prepare the sodium salt of the tosylhydrazone.

To the dry sodium salt was added 121.5 g. (1.48 moles) of cyclohexene and 246.3 g. (1.48 moles) of tetrachloroethylene. The resulting solution was heated at 100-105° for 15 hours. After washing the mixture with 5% hydrochloric acid and water, isolation of the crude product in the usual manner afforded 1.8 g. of a light yellow oil. Column chromatography of this material on 25 g. of silica gel gave, on elution with 300 ml. of hexane, 1.38 g. of a clear oil.

The NMR spectrum shows a sharp band at 5.62δ (60H) a sharp band at 5.12δ superimposed on a broad band centered at 5.21δ (60H) a sharp band at 5.02δ (15H), and a sharp band at 4.37δ (15H). This indicates a mixture consisting of approximately two parts of

3α-(2'-cyclohexenyl)-cholest-4-ene <u>134</u> and 3β-(2'-cyclohexenyl)-

cholest-4-ene <u>135</u>, two parts of spiro (4-cholestene-3, 1' -tetra-

chlorocyclopropane) <u>136</u>, one part endo-spiro (4-cholestene-3, 7'-

norcarane) <u>132</u>, and one part exo-spiro (4-cholestene-3, 7'-

norcarane) <u>133</u>.

The clear oil was then chromatographed on 12 g. of silica gel

impregnated with 1.2 g. of silver nitrate. Elution with 200 ml. of

20:1 hexane-benzene gave 0.688 g. of oil. Its NMR spectrum shows two

sharp bands due to olefinic protons at 5.12δ (53H) and 5.02δ (18H).

The integration shows this fraction to contain three parts spiro (4-

cholestene-3, 1'-tetrachlorocyclopropane) <u>136</u> and one part endo-

spiro (4-cholestene-3, 7'-norcarane) <u>132</u>. Elution with 15:1 hexane-

benzene (two 25 ml. fractions) gave 0.157 g. of exo-spiro (4-cholestene-

3, 7'-norcarane) <u>133</u>. The NMR shows one band due to an olefinic

proton at 4.37 δ. This data shows the ratio of addition products from

tetrachloroethylene and cyclohexene was 1.6 to 1.0, respectively.

<u>Cholestan-3-one p-Toluenesulfonylhydrazone <u>138</u>.</u> Cholestanone,

6.0 g. (0.0156 mole), and 3.0 g. (0.0161 mole) of tosylhydrazine were

added to 300 ml. of methanol. This mixture was heated on a steam

bath for 10 minutes and then allowed to stand at room temperature

overnight. The crystals which had formed were filtered affording

7.8 g. of white solid, m. p. 169-172° [lit. (15), 175-176°] .

<u>Pyrolysis of Cholestan-3-one p-Toluenesulfonylhydrazone <u>138</u></u>

with Sodium Methoxide in p-Xylene.   Cholestanone tosylhydrazone 138,

1.60 g. (0.0029 mole), and 12.6 ml. of 0.46 N sodium methoxide

(0.0058 mole) were employed in the usual fashion to form the sodium

salt of the tosylhydrazone.

Anhydrous p-xylene, 200 ml., was added to the sodium salt and

heated under reflux for 3 hours.   The reaction mixture was worked-

up in the usual manner affording 0.934 g. of a brown oil.   Thin layer

chromatography showed one band (R_f 0.85; hexane).   Column

chromatography of this oil on 20.0 g. of acid-washed alumina gave,

on elution with 150 ml. of hexane, 0.792 g. (90%) of crystalline

material specified as 2-cholestene 48.   Two recrystallizations from

acetone gave 0.510 g. of white needles, m.p. 72-73.5°, [lit. (124),

m.p. 75°].

The infrared spectrum of 48 is identical to the spectrum of an

authentic sample of 2-cholestene.

Pyrolysis of Cholestan-3-one p-Toluenesulfonylhydrazone 138

with Sodium Methoxide in Tetrachloroethylene.   To 2.0 g. (0.0036

mole) of cholestanone was added 15.8 ml. of 0.46 N sodium methoxide

(0.0072 mole).   This mixture was used in the usual way to form the

sodium salt of the tosylhydrazone.

To the dry sodium salt was added 200 ml. of tetrachloroethylene.

The resulting solution was heated under reflux for five hours.   The

cooled tetrachloroethylene solution was worked-up in the usual way to

give 1.784 g. of a brown oil. Thin layer chromatography (hexane)

showed two bands (R_f 0.87, 0.28). The more polar band did not

develop well, and was observable only after heating the sprayed plate

for two hours. Thin layer chromatography on silica gel impregnated

with silver nitrate showed two bands (R_f 0.66, 0.55; hexane).

The oily mixture was chromatographed on 30 g. silica gel

impregnated with 3 g. of silver nitrate. Elution with hexane (fractions

1 through 3) afforded 0.336 g. (24%) of crystalline solid identified as

a 4:1 mixture 142 of 3-(trichloroethylene)-cholest-2-ene and 3-

(trichloroethylene)-cholest-3-ene. Recrystallization from acetone

gave 0.255 g. of white needles, 134-135°. The NMR was unchanged

from that of the original solid.

<u>Anal</u>. Calcd. for $C_{29}H_{45}Cl_3$: C, 69.65; H, 9.07; Cl, 21.26

Found: C, 69.63; H, 8.89; Cl, 21.20

The infrared spectrum shows strong bands at 950 cm^{-1} and

861 cm^{-1}. The ultraviolet spectrum shows strong end absorption

with a shoulder at 248 mμ, ϵ = 5,500. The NMR shows broad bands

at 5.9δ (4H) and 5.65δ (1H) and sharp bands at 56 c.p.s. and 49.5

c.p.s. (26- and 27-Me), 47.5 c.p.s. (19-Me) and 41 c.p.s. (18-Me).

Elution with 10:1 hexane-benzene (fractions 4 through 6) pro-

vided 0.823 g. (58%) of a white solid identified as spiro (Nβ-tetra-

chlopyrazoline-3', 3-cholestane) 141. Recrystallization from acetone

gave 0.668 g. of fine needles, m.p. 165-166° α]$_D$ +26°.

Anal. Calcd. for $C_{29}H_{46}N_2Cl_4$: C, 61.18; H, 8.09; N, 4.92;

Cl, 25.81

Found: C, 61.30; H, 8.21; N, 5.16;

Cl, 25.67

The infrared spectrum displays a strong band at 770 cm^{-1}. The

NMR spectrum shows sharp bands at 55.5 c.p.s. (19,26 and 27-Me),

50 c.p.s. (26,27-Me) and 41 c.p.s. (18-Me).

Continued elution with 10:1 hexane-benzene gave 0.151 g. (10%)

of an oil identified as 2-cholestene 48. Recrystallization from acetone

gave 0.095 g. of needles, m.p. 70-73° [lit. (124), m.p. 75°].

The infrared spectrum of 48 is identical to that of an authentic

sample of 2-cholestene.

Further elution with benzene gave 0.115 g. of a white solid.

Thin layer chromatography indicated this to consist of a mixture of

at least three components. This fraction was discarded.

Alumina-catalyzed Conversion of Spiro (Nβ-tetrachloro-

pyrazoline-3', 3-cholestane) 141 to 2-Cholestene 48. Pyrazoline 141,

0.100 g., was added as a hexane solution to 4 g. of neutral alumina

and allowed to stand for 6 hours. Elution with 10:1 hexane-benzene

provided 0.072 g. of white solid. Recrystallization from acetone

gave white needles m.p. 71-73° [lit. (124), m.p. 75°]. This

material was identified as 2-cholestene.

The infrared spectrum of this material is identical to that of an

authentic sample of 2-cholestene.

Photolysis of Spiro (Nβ-tetrachloropyrazoline-3', 3-cholestane)

141. The spiro compound 141, 0.380 g., was dissolved in 260 ml.

of pentane and irradiated through a pyrex filter for 4 hours. Removal

of the pentane in vacuo afforded 0.257 g. of a yellow oil. Thin layer

chromatography (hexane) showed one major band (R_f 0.87). Column

chromatography of this oil on 10 g. of silica gel gave, on elution

with hexane (fractions 2 and 3), 0.199 g. of a clear oil shown to be

2-cholestene 48. Recrystallization from acetone gave 0.123 g. of

white needles, m.p. 70-73° [lit. (124), m.p. 75°].

The infrared spectrum is identical to the spectrum of an authentic

sample of 2-cholestene.

19-Nor- androst-4-ene-17β-ol-17-acetate-3-one p-Toluene-

sulfonylhydrazone 146. A solution of 5.0 g. (0.010 mole) of 19-nor-

testosterone acetate, 1.9 g. (0.010 mole) of tosylhydrazine and 100

ml. of methanol was stirred overnight at room temperature. Removal

of the solvent in vacuo gave a clear oil which could not be crystallized.

The infrared spectrum exhibits significant bands at 1340 cm^{-1},

1160 cm^{-1} and 810 cm^{-1}. The ultraviolet spectrum shows maxima at

262 mμ, ϵ = 13,800 and 226 mμ, ϵ = 11,400.

Pyrolysis of 19-Nor-androst-4-ene-17β-ol-17-acetate-3-one

p-Toluenesulfonylhydrazone 146 with Sodium Methoxide in Diglyme.

To 50 ml. of anhydrous methanol was added 2.09 g. (0.0043 mole) of 19-nor-testosterone acetate tosylhydrazone and 9.5 ml. of 0.45 N sodium methoxide (0.0043 mole). The methanol was removed in vacuo and the residual salt was dried overnight at 0.05 mm. Anhydrous diglyme (ca. 250 ml.) was distilled onto the sodium salt. The resulting solution was heated at 95° for twelve hours. The reaction was worked-up in the usual way affording 1.37 g. of a yellow oil. Thin layer chromatography indicated the presence of four components (R_f 0.67, 0.54, 0.49, 0.23; benzene-ethylacetate 4:1). Column chromatography of 1.30 g. of this mixture on 45 g. of silica gel, gave an elution with benzene, 0.283 g. (fractions 1 through 5) of an oil. Recrystallization from methylene chloride-methanol gave 0.210 g. of plates, m.p. 107-108°, $a]_D$ +47° [lit. (105), m.p. 101-103°, $a]_D$ +43°] .

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39

Found: C, 80.17; H, 9.36

The ultraviolet spectrum shows a maximum at 268 mμ, ϵ = 6,200. The infrared spectrum shows a band at 697 cm^{-1}, characteristic of a steroid 2,4-diene. The NMR exhibits a multiplet at 5.63δ, a triplet at 4.60δ and sharp bands at 1.98δ (acetate-Me), and 47.5 c.p.s. (18-Me). This data is consistent with the assigned structure, 19-nor-2,4-androstadiene-17β-ol-17-acetate 147.

4-Androstene-17β-ol-3-one p-Toluenesulfonylhydrazone **148**.

A solution of 11.4 g. (0.039 mole) of testosterone, 7.35 g. (0.039 mole) of p-toluenesulfonylhydrazine, and 200 ml. of methanol was stirred at room temperature for eight hours. Removal of the solvent in vacuo gave a clear oil which slowly solidified. Recrystallization from ether-hexane gave 14.3 g. of a granular solid, m.p. 124-129° (dec.). A further recrystallization from acetone-hexane gave the analytical sample, m.p. 130-134° (dec.).

Anal. Calcd. for $C_{26}H_{36}N_2SO_3$: C, 68.39; H, 7.95; N, 6.14

Found: C, 68.10; H, 7.89; N, 6.21

The infrared spectrum shows significant bands at 1340 cm^{-1} and 1160 cm^{-1}.

Pyrolysis of 4-Androstene-17β-ol-3-one p-Toluenesulfonylhydrazone **148** with Sodium Methoxide in Diglyme. To 100 ml. of anhydrous methanol was added 3.87 g. (0.0085 mole) of testosterone tosylhydrazone and 18.8 ml. of 0.45 N sodium methoxide (0.0085 mole). The methanol was removed in vacuo and the residual salt was dried overnight at 0.05 mm. Anhydrous diglyme (ca. 250 ml.) was distilled onto the sodium salt and the resulting solution was heated at 95° for 12 hours. The cooled solution was added to 1.3 l. of ice-water and extracted with ether. The combined organic layers were washed ten times with ca. 50 ml. portions of water and dried over magnesium sulfate. Removal of the ether in vacuo gave 2.42 g. of a

yellow oil. Thin layer chromatography indicated the presence of four

components (R_f 0.52, 0.42, 0.37, 0.33; benzene-ethyl acetate, 1:1).

Column chromatography of 2.40 g. of this mixture on 60 g. of silica

gel gave, on elution with 5:1 benzene-ether (fractions 3 through 6),

0.486 g. of a white solid identified as 2,4-androstadiene-17β-ol 149.

Sublimation of the white solid gave 0.378 g. of crystals, m.p. 169-

171° [lit. (6), m.p. 171-173°] .

The ultraviolet spectrum displays a maximum at 266 mμ, ε =

5,100. The infrared spectrum shows a band at 692 cm^{-1} character-

istic of steroid 2,4-dienes. The NMR spectrum shows a multiplet at

5.63δ typical of steroid 2,4-dienes, a broad band at 3.66δ and sharp

bands at 57 c.p.s. (19-Me) and 47 c.p.s. (18-me).

Pyrolysis of 4-Androstene-17β-ol-17-acetate-3-one p-Toluene-

sulfonylhydrazone 150 with Sodium Hydride in Tetrachloroethylene.

A mixture of testosterone acetate tosylhydrazone, 8.0 g. (0.016 mole),

sodium hydride, 1.0 g. (0.040 mole), and 700 ml. of tetrachloro-

ethylene was heated under reflux until nitrogen evolution ceased. The

sodium hydride was removed by gravity filtration and removal of the

solvent in vacuo afforded 5.2 g. of a red oil. Column chromatog-

raphy of this oil on 60 g. of silica gel gave, on elution with 6:1 benzene-

ether, 3.37 g. (63%) of white crystals. This material was identified

as spiro (tetrachlorocyclopropane-1', 3-androst-4-ene-17β-ol-17-

acetate) 151. Recrystallization from acetone gave 2.81 g. of white

needles, m. p. 160-162°, α] $_D$ $^{+99°}$.

Anal. Calcd. for $C_{23}H_{34}Cl_4O_2$: C, 57.55; H, 6.24; Cl, 29.52

Found: C, 57.32; H, 6.46; Cl, 29.27

The NMR spectrum shows a sharp band at 5.16δ (1H), a triplet

centered at 4.53δ (1H), and sharp bands at 118 c.p.s. (acetate

methyl), 66 c.p.s. (19-Me) and 47.5 c.p.s. (18-Me). The ultra-

violet spectrum shows a maximum at 206 mμ, ε = 13,700. The

infrared spectrum shows bands at 840 cm^{-1}, 855 cm^{-1} and 870 cm^{-1}.

1-Cholesten-3-one p-Toluenesulfonylhydrazone 58. To a solu-

tion of 1.0 g. (0.005 mole) of p-toluenesulfonylhydrazine in ca. 150

ml. of methanol was added 2.0 g. (0.005 mole) of 1-cholesten-3-one.

The solution was stirred as the tosylhydrazone slowly precipitated

over a ten hour period. The white precipitate was filtered and

recrystallized from methanol providing 2.2 g. of compact needles,

m. p. 173-176° [lit. (16), m.p.162°] .

Anal. Calcd. for $C_{34}H_{52}N_2O_2S$: C, 73.86; H, 9.48; N, 5.07

Found: C, 73.78; H, 9.49; N, 5.11

The ultraviolet spectrum shows maxima at 257 mμ, ε = 14,500

and 229 mμ, ε = 13,900. The infrared spectrum shows significant

bands at 3200 cm^{-1}, 1330 cm^{-1}, and 1160 cm^{-1}.

Pyrolysis of 1-Cholesten-3-one p-Toluenesulfonyl-

hydrazone 58 with Sodium Methoxide in Benzene. 1-Cholesten-3-one

tosylhydrazone, 1.0 g. (0.0018 mole), and 7.72 ml. of 0.47 N

sodium methoxide (0.0036 mole) were used in the usual way to form

the sodium salt of the tosylhydrazone.

Anhydrous benzene, 150 ml., was added to the dry sodium salt

and the resulting solution was heated at an oil bath temperature of

110° for 15 hours. The crude product was isolated in the usual way

to give 0.66 g. of a yellow oil.

Thin layer chromatography showed the presence of two non-

polar components (R_f 0.75, 0.52; hexane) and four polar components

of which two were predominant (R_f 0.72, 0.61; benzene-ethyl acetate,

19:1). The crude oil was chromatographed on 15 g. of silica gel.

Elution with hexane (fractions 2 through 5) provided 0.23 g. (35%) of

an oil identified as 1, 3-cholestadiene 152. Low temperature recrystal-

lization from ether gave 0.19 g. of white solid, m.p. 64-66°, $\alpha]_D$

+74° [lit. (94), m.p. 67°, $\alpha]_D$ + 73°].

The infrared spectrum shows a weak band at 3020 cm^{-1} and a

strong band at 698 cm^{-1} indicative of a 1, 3-steroid diene. The ultra-

violet spectrum exhibits a maximum at 262 mμ, ϵ = 3,900 (hexane).

The NMR spectrum displays a complex olefin band centered at 5.83δ

and sharp bands at 40 c.p.s. (18-Me), 46.5 c.p.s. (19-Me), and at

56 c.p.s. and 49.5 c.p.s. (26- and 27-Me).

Further elution with hexane (fractions 7 through 13) afforded

0.32 g. (48%) of white solid identified as spiro (cycloheptatriene-7', 3-

cholest-1-ene) <u>153</u>. Recrystallization from methanol-chloroform

provided 0.29 g. of fine white needles, m. p. 96-97°, a] $_D$ -20°.

<u>Anal</u>. Calcd. for $C_{33}H_{50}$: C, 88.70; H, 11.28

Found: C, 88.91; H, 11.33

The infrared spectrum displays a weak band at 3020 cm^{-1} and

strong bands at 750 cm^{-1}, 727 cm^{-1}, 690 cm^{-1} and 685 cm^{-1}. The

ultraviolet spectrum shows a maximum at 271 mµ, ϵ = 2,750. The

NMR spectrum shows multiplets centered at 6.30δ (2H) and 5.95δ

(2H), an AB quartet centered at 5.46δ, J = 10 c.p.s. with the A

proton at 5.69δ and the βproton at 5.25 δ, a doublet at 4.50δ (2H),

and sharp bands at 56 c.p.s. (26- and 27-Me) 50 c.p.s. (19-, 26-

and 27-Me), and 40 c.p.s. (18-Me).

Elution with 3:1 hexane-benzene (fractions 18 through 26) gave

0.050 g. (8%) of an oil identified as cholest-1-ene-3a-ol-3-methyl

ether <u>154</u>. Low temperature recrystallization from methanol-ether

provided 0.035 g. of a white solid, m. p. 64-66°, a] $_D$ +12°.

<u>Anal</u>. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07

Found: C, 84.04; H, 12.22

The infrared spectrum shows bands at 3020 cm^{-1}, 2830 cm^{-1},

1080 cm^{-1} and 1070 cm^{-1}. The NMR spectrum exhibits a multiplet

centered at 5.82δ (2H), a broad band at 3.48δ (1H) due to the 3β-

proton, and sharp bands at 3.28δ (-OMe), 46.5 c.p.s. (19-Me) and

40.5 c.p.s. (18-Me) and 50 c.p.s. and 56 c.p.s. (26- and 27-Me).

A fourth component, 0.024 g. (4%), was eluted with 2:1 hexane-benzene (fractions 28 through 34) and identified as cholest-2-ene-3β-ol-3-methyl ether **155**. Recrystallization from methanol-chloroform afforded 0.011 g. of white needles, m.p. 72-73°, a]$_D$ +40°.

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07

Found: C, 83.76; H, 12.01

The infrared spectrum shows bands at 3020 cm^{-1}, 2830 cm^{-1}, 1100 cm^{-1} and 1080 cm^{-1}. The NMR spectrum displays a broadened quartet centered at 5.65δ (2H), a broad band at 3.80δ due to the 3α-proton, and sharp bands at 3.22δ (-OMe), 53.5 c.p.s. (19-Me), 40 c.p.s. (18-Me) and 50 c.p.s. and 55 c.p.s. (26- and 27-Me).

This reaction was repeated under the same conditions with 10 ml. of methanol added to the pyrolysis mixture. These conditions gave **154** and **155** (59%) as the only major products along with recovered tosylhydrazone **58** (41%).

Pyrolysis of 1-Cholesten-3-one p-Toluenesulfonylhydrazone **58** with Sodium Hydride in Benzene. Sodium hydride, 1.78 g. (0.037 mole) was added to a solution of 1-cholesten-3-one tosylhydrazone, 4.0 g. (0.0072 mole), and 300 ml. of anhydrous benzene. The resulting mixture was heated at an oil bath temperature of 110° for 15 hours. The excess sodium hydride was removed from the cooled solution by gravity filtration. The benzene solution was worked-up in the usual

way and gave 3.20 g. of a yellow oil. Thin layer chromatography showed two predominant non-polar bands (R_f 0.74, 0.52; hexane). The crude oil was chromatographed on 50 g. of silica gel. Elution with hexane provided 0.73 g. (23%) of 1,3-cholestadiene 152 and 0.90 g. (29%) of spiro (cycloheptatriene-7', 3-cholest-1-ene) 153.

The remainder of the material on the column was removed with ether and gave 1.48 g. (48%) of a yellow oil. This oil was not analyzed.

Alumina-catalyzed Aromatization of Spiro (cycloheptatriene-7', 3-cholest-1-ene) 153. A hexane solution of steroid spiroheptatriene 153, 0.10 g., was added to 10.0 g. of neutral alumina, 10.0 g. of basic alumina, and 10.0 g. of acid-washed alumina. In each case the spiroheptatriene was left on the column for 2 hours. Elution with 50 ml. of 5:1 hexane-benzene gave 0.094 g. of crystals from neutral alumina, 0.092 g. of crystals from basic alumina, and 0.092 g. of oil from acid washed alumina.

The products from neutral and basic alumina were identical in every respect and were shown to be 3-phenyl-cholest-2-ene 124. Recrystallization of either product from acetone gave ca. 0.080 g. of long white needles, m.p. 139-140° [lit. (131) m.p. 126-127°; lit. (128), anisotropic liquid 132° and m.p. 144°]. The infrared spectra shows a weak band at 3020 cm^{-1} and strong bands at 748 cm^{-1} and 690 cm^{-1}. The infrared spectra were identical with the infrared

spectrum of an authentic sample of 3-phenyl-cholest-2-ene. The

ultraviolet spectra display a maximum at 248 mμ, ϵ = 12,500. The

NMR spectra show a band at 7.25δ, a broad band at 6.02δ, and sharp

bands at 48.0 c.p.s. (19-Me) and 40.5 c.p.s. (18-Me).

The NMR spectrum of the product from acid-washed alumina

shows it to be 83% starting material 153 and 17% of an aromatic com-

ponent, presumably 3-phenyl-cholest-2-ene 124.

Alumina-catalyzed Reaction of Cholest-1-en-3a-ol-3-methyl

ether 154. Cholest-1-en-3a-ol-3-methyl ether, 0.24 g., was added

as a hexane solution to a column of 10 g. of neutral alumina and

allowed to stand for 2 hours. Elution with 50 ml. of hexane gave

0.045 g. (21%) of an oil identified as 1,3-cholestadiene. Thin layer

chromatography showed this material to have the same R_f value as that

of 152, (R_f 0.75; hexane).

The ultraviolet spectrum shows a maximum at 262 mμ, ϵ =

3600.

Elution with benzene gave 0.018 g. (8%) of a yellow oil which

was discarded. Further elution with ether gave 0.155 g. (71%) of

solid shown to be a mixture 151 of cholest-1-en-3a-ol and cholest-1-

en-3β-ol. Thin layer chromatography of this material and an

epimeric mixture of cholest-1-en-3-ols showed identical retnetion

times (R_f 0.25, 0.15; ethyl-acetate benzene, 1:1).

The infrared spectrum displays the same bands as the infrared

spectrum of a known mixture of cholest-1-en-3α-ol and cholest-1-en-3β-ol.

Alumina-catalyzed Reaction of Cholest-1-en-3β-ol-3-methyl ether 155. To a column of 10 g. of neutral alumina was added 0.08 g. of cholest-1-en-3β-ol-3-methyl ether as a hexane solution. After 2 hours, elution with 50 ml. of hexane gave 0.006 g. (8%) of an oil identified as 1,3-cholestadiene.

The ultraviolet spectrum shows a maximum at 262 mμ, ϵ = 3900.

Elution with 50 ml. of benzene gave 0.006 g. (8%) of a yellow oil which was discarded. Elution with 50 ml. of ether afforded 0.056 g. (84%) of a white solid shown to consist of cholest-1-en-3α-ol and cholest-1-en-β-ol by comparison of retention times on thin layer chromatography and by comparison of infrared spectra with an authentic sample.

Cholest-1-en-3α-ol and Cholest-1-en-3β-ol 157. A mixture of cholest-1-en-3-one, 0.50 g. (0.0013 mole), 50 ml. of anhydrous ether and 0.050 g. (0.0013 mole) of lithiumaluminumhydride was heated under reflux overnight. The excess hydride was destroyed with methanol and the mixture was poured into a concentrated solution of sodium potassium tartrate. The organic layer was dried over magnesium sulfate and the ether was then removed in vacuo to give 0.49 g. of a white solid.

The infrared spectrum shows a broad band at 3420 cm^{-1}, a weak band at 1625 cm^{-1} and strong bands at 1200 cm^{-1} and 1020 cm^{-1}.

2-Cholesten-1-one p-Toluenesulfonylhydrazone <u>178</u>. To a solution of 0.60 g. (0.0016 mole) of 2-cholestene-1-one in 60 ml. of methanol was added 0.40 g. (0.0021 mole) of p-toluenesulfonylhydrazine and three drops of concentrated hydrochloric acid. The resulting solution was heated under reflux for two and one-half hours. Approximately one-half of the solvent was removed <u>in vacuo</u>. The concentrated solution was poured into water and extracted with ether. The ether extracts were washed with 5% sodium bicarbonate and dried over magnesium sulfate. Removal of the ether afforded a light yellow oil. Trituration of this oil with methanol gave 0.61 g. of white needles, m.p. 73-78°.

<u>Anal</u>. Calcd. for C$_{34}$H$_{52}$N$_2$O$_2$S: C, 73.86; H, 9.48

Found: C, 73.86; H, 9.52

The ultraviolet spectrum shows maxima at 268 mμ, ϵ = 8,300, and 226 mμ, ϵ = 14,300. The infrared spectrum displays bands at 3220 cm^{-1}, 1340 cm^{-1} and 1160 cm^{-1}.

Pyrolysis of 2-Cholesten-1-one p-Toluenesulfonylhydrazone <u>178</u> with Sodium Methoxide in Diglyme. To a mixture of 0.441 g. (0.0008 mole) of tosylhydrazone <u>178</u>, and 50 ml. of anhydrous methanol was added 3.0 ml. of 0.26 N sodium methoxide (0.0008 mole). This

mixture was used in the usual manner to form the sodium salt of the tosylhydrazone. Diglyme, ca. 60 ml., was distilled onto the sodium salt. The resulting solution was heated at an oil bath temperature of 130° until all nitrogen evolution ceased. The cooled diglyme solution was poured into water and extracted with ether. The combined ether layers were repeatedly washed with water. After the organic layers had been dried over magnesium sulfate, the solvent was removed _in vacuo_ affording 0.302 g. of a brown oil. Thin layer chromatography gave three bands which showed nearly the same retention times (R_f 0.93, 0.91, 0.88; hexane). Thin layer chromatography on silica gel impregnated with silver nitrate gave increased separation of the bands (R_f 0.93, 0.60, 0.31; hexane-benzene, 8:1). Column chromatography on silica gel gave, on elution with hexane, 0.148 g. (49%) of a white solid. Crystallization from ether gave 0.078 g. of a component as a white powder, m.p. 184-187°. Analysis and molecular weight determinations indicated this compound was a dimer.

<u>Anal.</u> Calcd. for: $C_{27}H_{44}$: C, 87.97; H, 12.03

Found: C, 87.99; H, 11.94

<u>Mol. Wt.</u> Calcd. for: 736 a.m.u.

Found: 690 a.m.u.

The ultraviolet spectrum shows no maximum above 210 mμ.

The NMR shows a broad band at 5.7 δ and sharp bands at 55 c.p.s.

49 c. p. s. , and 40 c. p. s.

Column chromatography of the mother liquors (0.070 g.) gave at least four more non-polar products which were not analyzed further.

2-Androsten-1-one p-Toluenesulfonylhydrazone 159. A solution of 0.50 g. (0.0018 mole) of 2-androsten-1-one, 2.00 g. (0.0107 mole) of tosylhydrazine, 3 drops of concentrated hydrochloric acid and 60 ml. of methanol was heated under reflux for 3 hours. The solution was poured into 200 ml. of water and extracted with ether. Removal of the ether gave 0.950 g. of a yellow oil. Thin layer chromatography showed two bands, both having different retention times than the starting ketone. Crystallization from methanol gave 0.207 g. of a white solid, m. p. 145-147°.

The ultraviolet spectrum shows no maximum above 220 mμ. The NMR spectrum shows a multiplet centered at 7.55 δ (8H), a sharp band at 2.45 δ (6H), and sharp bands at 42 c. p. s. (3H) and 59 c. p. s. (3H) attributable to angular methyl groups. This data is consistent with a steroid structure which has added two molecules of tosyl-hydrazine, presumably at C-1 and C-3.

The mother liquors were condensed and more of the impurity was allowed to crystallize out. Thin layer chromatography of the oil, 0.531 g. , recovered from the mother liquors showed one major band and a very minor band corresponding to the high melting impurity. This oil resisted all attempts at crystallization.

The ultraviolet spectrum shows maxima at 268 mμ, ϵ = 5,100

and 226 mμ, ϵ = 13,000. The infrared spectrum shows no carbonyl

absorption and a significant band at 1160 cm^{-1}. This data is con-

sistent with the desired tosylhydrazone, 2-androsten-1-one p-

toluenesulfonylhydrazone 159.

Pyrolysis of 2-Androsten-1-one p-Toluenesulfonylhydrazone 159

with Sodium Methoxide in Diglyme. A methanol solution of 4.1 g.

(0.0093 mole) of 2-androsten-1-one tosylhydrazone and 17.5 ml. of

0.53 N sodium methoxide (0.0093 mole) was used in the usual manner

to form the sodium salt of the tosylhydrazone.

Anhydrous diglyme, 600 ml., was distilled onto the sodium

salt and then heated at 135° for 8 hours. The diglyme solution was

poured into water and extracted with hexane. The organic layers were

repeatedly washed with water and then dried over magnesium sulfate.

Removal of the hexane gave 2.36 g. of a light yellow oil. Column

chromatography on 45 g. of silica gel gave 0.95 g. (40%) of non-

polar (200 ml. of hexane) and 1.20 g. of polars (200 ml. of ether).

Thin layer chromatography of the non-polars on silica gel impregnated

with silver nitrate gave at least five bands (R$_f$ 0.93, 0.78, 0.41, 0.22,

and 0.14; 10:1 hexane-benzene). Column chromatography of the

non-polar fraction on 30 g. of silica gel impregnated with silver

nitrate gave, on elution with 6:1 hexane-benzene (fractions 21 through

26), 0.156 g. of white solid. Recrystallization from chloroform

methanol gave a crystalline solid, m.p. 195-197°, identified only as

a dimer.

Anal. Calcd. for: $C_{19}H_{28}$: C, 88.99; H, 11.01

Found: C, 88.84; H, 11.10

Mol. Wt. Calcd. for: 512 a.m.μ

Found: 513 a.m.μ

The ultraviolet spectrum shows no maximum above 210 mμ.

The NMR spectrum shows a quartet centered at 5.7δ and sharp bands

at 50 c.p.s. (19-Me) and 43 c.p.s. (18-Me).

Elution with benzene (fractions 31 and 32) gave another dimer,

0.105 g., as a white solid. Recrystallization from methanol-

chloroform gave a white powder, m.p. 265-267°.

Anal. Calcd. for: $C_{19}H_{28}$: C, 88.99; H, 11.01

Found: C, 88.94; H, 11.03

Mol. Wt. Calcd. for: 512 a.m.μ

Found: 519 a.m.μ

The ultraviolet spectrum shows no maxima above 210 mμ. The

NMR spectrum shows a quartet centered at 5.6δ and sharp bands at

49.5 c.p.s. (19-Me) and 43 c.p.s. (18-Me). The structure of this

dimer was not determined.

Further elution with benzene (fraction 33) gave one more dimer,

0.065 g., as a white solid. Recrystallization from methanol

chloroform gave a white solid, m.p. 188-190°.

<u>Anal</u>. Calcd. for: $C_{19}H_{28}$: C, 88.99; H, 11.01

Found: C, 88.91; H, 11.12

<u>Mol. Wt</u>. Calcd. for: 512 a.m.u.

Found: 513 a.m.u.

The ultraviolet spectrum shows no maximum above 210 mμ.

The NMR spectrum shows a multiplet at 5.6δ and sharp bands at

48 c.p.s. (19-Me) and 43.5 c.p.s. (18-Me).

The polar fraction was chromatographed on 12 g. of silica gel.

Elution with 3:1 hexane-benzene gave 0.298 g. of an oil identified as

a mixture of 3-cholestene-1α-ol-1-methyl ether and 2-cholestene-1β-

ol-1-methyl ether.

The NMR spectrum shows two broad bands at 5.85δ and 5.60δ,

and two sharp bands at 3.30δ and 3.27δ, and bands due to angular

methyl groups at 42 c.p.s. and 44 c.p.s.

Further elution with benzene gave an oil 0.366 g. which was

identified as products resulting from insertion of the intermediate

carbene into the carbon-hydrogen bands of diglyme. The NMR

spectrum shows, in addition to the bands of the angular methyl groups,

a multiplet centered at 5.7δ and sharp bands at 3.61δ and 3.39δ.

Pyrolysis of 2-Androsten-1-one p-Toluenesulfonylhydrazone <u>159</u>

<u>with Sodium Methoxide in benzene</u>. A methanol solution of 2.0 g.

(0.0045 mole) of 2-androsten-1-one tosylhydrazone and 20.0 ml. of

0.46 N sodium methoxide (0.0045 mole) was used in the usual way to

form the sodium salt of the tosylhydrazone.

To the dry sodium salt was added 1 l. of benzene, and this solution was heated under reflux for 15 hours. Work-up of this reaction in the usual manner afforded 1.26 g. of yellow oil. Thin layer chromatography indicated two non-polar components (R_f 0.80, 0.75; hexane). Column chromatography of this material on 30 g. of silica gel gave, on elution with hexane (fractions 4 and 5; 10 ml. fractions), 0.128 g. (10%) of an oil. Thin layer chromatography showed this material to be a mixture of two components. Its NMR spectrum gave no bands indicative of a spirotropilidine which might have resulted from addition of an intermediate to benzene. Further elution with hexane (fractions 6 and 7) gave 0.188 g. (16%) of an oil identified as 1β,10β-methylene-androst-2-ene <u>160</u>.

The ultraviolet spectrum shows no maximum above 207 mμ. The NMR spectrum shows a pair of multiplets centered at 5.9δ and 5.4δ and one sharp band at 41 c.p.s. due to the C-18 angular methyl group.

<u>5-Androstene-3β-ol</u> <u>II-94</u>. A solution of dehydroepiandrostenone (60 g., 0.208 mole) in 1 l. of dithethylene glycol, 300 ml. of n-butanol and 200 ml. of 95% hydrazine was heated under reflux in a nitrogen atmosphere for 2 hours. After cooling the mixture to room temperature, 80 g. (1.43 moles) of potassium hydroxide was added. The temperature of the solution was raised to 200-203° by codistillation

of the solvents. The reaction was allowed to remain at this tem-
perature for 4 hours. The cooled mixture was poured into 3 l. of
ice-water and the precipitate filtered. The resulting solid was
dissolved in ether and washed with 5% hydrochloric acid solution and
dried over magnesium sulfate. Removal of the solvent in vacuo
afforded 55.7 g. of a white powder, m.p. 129-133°. Recrystalliza-
tion from acetone gave 48.0 g. of needles, m.p. 134-136° [lit. (116),
m.p. 133-134°].

Androstan-3β-ol II-95. To 10.0 g. (0.0364 mole) of 5-
androstene-3β-ol in 250 ml. of ethyl acetate was added 0.1 g. of
platinum oxide and 3 drops of perchloric acid. This solution was
hydrogenated on a Paar low pressure apparatus at an initial pressure
of 48 p.s.i. The pressure became constant at 44.5 p.s.i. after 1
hour and the catalyst was removed by gravity filtration. The ethyl
acetate solution was washed with 5% sodium bicarbonate, water and
dried over magnesium sulfate. Removal of the solvent in vacuo gave
7.8 g. of white needles, m.p. 142-146° [lit. (60), m.p. 148-149°].

Androstanone II-96. To a 5 l. three-necked round bottom flask
equipped with stirrer and dropping funnel was added 134 g. (0.511
mole) of sodium dichromate dissolved in 415 ml. of water followed by
the addition of 164 ml. of conc. sulfuric acid and 92 ml. of glacial
acetic acid. This mixture was cooled to 0° in an ice bath.

Androstanol (100 g., 0.362 mole) was dissolved in 1.5 1. of

benzene and added to the oxidizing medium from a dropping funnel

over a 1.5 hour period. After the androstanol had been added, the

stirring was continued for eight hours at room temperature. The

mixture was placed in a separation funnel and the oxidizing solution

was separated. The organic layer was washed with 5% sodium

bicarbonate solution, water and dried over magnesium sulfate.

Removal of the solvent in vacuo afforded 86 g. of a yellow oil.

Crystallization from methanol gave 47 g. of needles, m.p. 100-101°.

[lit. (60), m.p. 102-102.5°]. The solvent was removed from the

mother liquor to give a yellow oil. Sublimation of this oil at 90° and

0.1 mm. gave a white solid. Recrystallization of this solid from

methanol afforded 19.0 g. of white needles, m.p. 100-101°.

The infrared spectrum shows a strong band at 1714 cm^{-1}.

2α-Bromo-Androstan-3-one II-97. Androstanone 20 g. (0.073

mole) was dissolved in 100 ml. of glacial acetic acid. After the

solution was cooled to ca. 15° in a cold water bath, 73 ml. of a

1.00 M solution of bromine in glacial acetic acid was added. The

solution slowly decolorized and after 45 minutes the white precipitate

was filtered. Recrystallization from methanol-chloroform gave 21 g.

of white needles, m.p. 205-208° [lit. (37), m.p. 210-211.5°].

The infrared spectrum displays a strong band at 1714 cm^{-1}.

The NMR spectrum displays, as part of an HMX pattern, a quartet

centered at 4.77δ (J = 6 c.p.s.) and a quartet centered at 2.65δ

(J = 6 c.p.s.). The NMR spectrum also shows sharp bands at 66

c.p.s. (19-Me) and 44 c.p.s. (18-Me).

1-Androsten-3-one II-98. 2α-Bromo-androstan-3-one, 5.0 g.

(0.014 mole), 4.0 g. (0.040 mole) of calcium carbonate and 50 ml.

dimethyl acetamide were heated under reflux for 20 minutes. The

calcium carbonate was removed by filtration and the filtrate poured

into ice and 5% hydrochloric acid solution and extracted with ether.

The organic layers were washed with water and dried over magnesium

sulfate. The solvent was removed in vacuo affording 3.6 g. of light

yellow oil. Thin layer chromatography (benzene-ethyl acetate, 6:1)

indicated one major component (R_f 0.55). Column chromatography

on 120 g. of acid washed alumina gave 3.4 g. of crystalline material

(hexane-benzene, 2:1; fractions 5 through 13). Recrystallization from

hexane gave 2.5 g. of white needles, m.p. 104-105° [lit. (112), m.p.

102-103°].

The infrared spectrum shows a strong band at 1680 cm^{-1}

attributate to an α, β-unsaturated carbonyl. The ultraviolet spectrum

shows a maximum at 230 mμ, ε = 14,900. The NMR spectrum shows

an AB quartet centered at 6.50δ and sharp bands at 62 c.p.s. (19-Me)

and 45 c.p.s. (18-Me).

1α,2α-Oxido-Androstanone II-99. 1-Androsten-3-one, 10.0 g.

(0.037 mole), 100 ml. of 30% hydrogen peroxide, 250 ml. of ethanol

and 2 ml. of 40% sodium hydroxide were refluxed for 10 minutes on the steam bath. The cooled solution was diluted with ether and poured into ca. 1.5 l. of water. The water layer was extracted five times with ether. The combined organic layers were repeatedly washed with water and then dried over magnesium sulfate. Removal of ether in vacuo gave 10.1 g. of an oil. Recrystallization from aqueous ethanol afforded 9.1 g. of white powder, m.p. 101-104° [lit. (103), m.p. 104-105°].

The infrared spectrum shows significant bands at 1700 cm^{-1} and 870 cm^{-1}. The NMR spectrum displays an AB quartet centered at 3.3δ (J = 4 c.p.s.) and sharp bands at 54 c.p.s. (19-Me) and 44.5 c.p.s. (18-Me).

2-Androsten-1α-ol II-100. A solution of 11.0 g. (0.039 mole) of 1α,2α-oxido-androstanone, and 125 ml. of 100% hydrazine hydrate was heated under reflux for 15 minutes. The cooled solution was poured onto 5% hydrochloric acid and ice, and extracted with ether. Isolation of the crude product in the usual manner afforded 9.2 g. of a red oil. Column chromatography on neutral alumina (Activity II) provided as the major fraction 6.8 g. of a red oil. This oil could not be crystallized and was used in the next reaction of the synthetic sequence without further purification.

The infrared spectrum displays strong bands at 3400 cm^{-1} and 1000 cm^{-1}.

2-Androsten-1-one <u>II-101</u>. A solution of 5. 50 g. of the crude

2-androstene-1α-ol in 800 ml. of acetone (distilled from potassium

permanganate) was cooled in an ice bath and rapidly stirred as 6. 5 ml.

of Jones reagent was added. After 10 minutes, the solution was poured

into ca. 1. 5 l. of saturated salt solution and extracted several times

with ether. The combined organic layers were washed with 5%

sodium bicarbonate solution and then worked-up in the usual manner

affording 5. 4 g. of a brown oil. This material was chromatographed

on 160 g. of acid washed alumina. Elution with benzene (fraction 1;

600 ml. of benzene) gave a colorless oil, 4. 9 g. , which quickly

crystallized. Recrystallization from hexane provided 4. 1 g. of long

white needles, m. p. 76-77° [lit. (103), m. p. 75-75. 5°] .

The infrared spectrum displays a significant band at 1670 cm^{-1}.

The ultraviolet spectrum shows a maximum at 225 mμ, ϵ = 8100.

The NMR spectrum exhibits a pair of triplets at 6. 60δ (1H) and a pair

of triplets at 5. 70δ (1H), and sharp bands at 62 c. p. s. (19-Me) and

43. 5 c. p. s. (18-Me).

5-Cholestene-3β-ol-3-acetate-7-one. To a mixture of 280 ml.

of glacial acetic acid and 160 ml. of acetic anhydride was added 40 g.

(0. 0935 mole) of cholesteryl acetate and 24. 0 g. (0. 292 mole) of

sodium acetate. The resulting solution was cooled to 35° and 35. 0 g.

(0. 216 mole) of sodium chromate was added portionwise over a 15

minute period. This solution was stirred for 46 hours at an oil bath

temperature of 50-60°. The reaction mixture was poured into 3.5 l. of cold water and stirred at 10° for 1 hour. After the precipitate had been filtered and washed with water, it was dissolved in benzene. This solution was dried over magnesium sulfate and chromatographed on 200 g. of acid-washed alumina to remove the green coloration. Elution with 1 l. of benzene gave 28.0 g. of white solid. Recrystallization from methanol gave 16.3 g. of white needles, m.p. 155-158°. Thin layer chromatography (4:1 benzene-ethyl acetate) showed a band attributable to 7-ketocholesteryl acetate (R_f 0.57) and a minor band due to an impurity (R_f 0.77). A further recrystallization from hexane-benzene gave 12.0 g. of white needles, m.p. 158.5-160° [lit. (44), 157-159°]. Thin layer chromatography of this material gave one band (R_f 0.59; 4:1 benzene-ethyl acetate).

The ultraviolet spectrum shows a maximum at 237 mμ, ε = 12,600.

5-Cholesten-3β-ol-3-acetate-7-one p-Toluenesulfonylhydrazone

54. Tosylhydrazine, 5.0 g. (0.027 mole), was added to a solution of 12.0 g. (0.027 mole) of 7-ketocholesteryl acetate in ca. 400 ml. of methanol. This mixture was heated under reflux for 2.5 hours. The solution was concentrated to ca. 175 ml. and allowed to cool to room temperature. Further cooling in a refrigerator gave 8.7 g. of white needles, m.p. 148-150° [lit. (16), 147-149°].

The ultraviolet spectrum shows maxima at 268 mμ, ε = 9,900

and 228 mμ, ϵ = 18,000. The infrared spectrum shows strong bands

at 3200 cm^{-1}, 1725 cm^{-1} and 1160 cm^{-1}.

The mother liquor from the above reaction was concentrated to

ca. 100 ml. and another 4.4 g. of white needles were isolated, m.p.

145-148° (dec.).

Pyrolysis of 5-Cholesten-3β-ol-3-acetate-7-one p-Toluene-

sulfonylhydrazone 54 with Lithium Hydride in Toluene.   Lithium

hydride, 0.4 g. (0.050 mole), and 0.418 g. (0.0007 mole) of 7-

ketocholesteryl acetate tosylhydrazone were added to ca. 40 ml. of

anhydrous toluene.   The resulting solution was heated under reflux

for 8 hours.   The lithium hydride was removed by gravity filtration

and the organic layer was washed five times with 20 ml. portions of

water and dried over magnesium sulfate.   The toluene was removed

in vacuo affording 0.261 g. of a light yellow crystalline mass.   Thin

layer chromatography (benzene-ethyl acetate, 6:1) showed only one

band (R$_f$ 0.71).   Recrystallization from methanol-chloroform gave

0.217 g. of white plates, m.p. 127-128°.   The properties of this

compound were identical to those of an authentic sample of 7-

dehydro-cholesteryl acetate 55.

Pyrolysis of 5-Cholesten-3β-ol-3-acetate-7-one p-Toluene-

sulfonylhydrazone 54 with Sodium Methoxide in Diglyme.   To 2.0 g.

(0.0033 mole) of 5-cholestene-3β-ol-3-acetate-7-one tosylhydrazone

was added 12.9 ml. of 0.26 N sodium methoxide (0.0033 mole).   This

mixture was used in the usual way to prepare the sodium salt of the tosylhydrazone. Diglyme, 50 ml., was distilled from lithium aluminum hydride onto the sodium salt. The resulting solution was heated for 2 hours at an oil bath temperature of 120°. The cooled diglyme solution was poured into ice-water and extracted with ether. The combined organic layers were washed ten times with 50 ml. portions of water and dried over magnesium sulfate. Removal of the solvent in vacuo afforded 1.144 g. of a yellow crystalline mass. Thin layer chromatography (benzene-ethyl acetate, 6:1) showed five peaks of which two were very predominant (R_f 0.74, 0.30). Thin layer chromatography also indicated the less polar component was 7-dehydro-cholesteryl acetate 55 while the more polar band corresponded to 7-dehydro-cholesterol 161.

The yellow product was chromatographed on 30 g. of silica gel. Elution with 8:1 benzene-ether (fractions 3 through 6) gave 0.716 g. (63%) of white crystalline material identified as 7-dehydro-cholesteryl acetate 55. Recrystallization from methanol-chloroform gave 0.607 g. of white plates, m.p. 126-128° [lit. (16), m.p. 129°].

The ultraviolet spectrum shows maxima at 293 mμ, ϵ = 5,700, 282 mμ, ϵ = 10,400, and 272 mμ, ϵ = 9,600.

Pyrolysis of 5-Cholesten-3β-ol-3-acetate-7-one p-Toluenesulfonylhydrazone 54 with Sodium Methoxide in Benzene. To 0.500 g. (0.0008 mole) of 5-cholesten-3β-ol-3-acetate-7-one-tosylhydrazone

was added 3.5 ml. of 0.46 N sodium methoxide (0.0016 mole). This

mixture was used in the usual way to form the sodium salt of the

tosylhydrazone. Anhydrous benzene, 200 ml., was added to the

sodium salt and this solution was heated under reflux for 15 hours.

Work-up in the usual manner gave 0.311 g. of a brown oil. Thin

layer chromatography of this material showed five bands of which two

were very predominant (R_f 0.75, 0.30; benzene-ethyl acetate, 6:1).

This thin layer chromatogram was identical to that from the pyrolysis

of 54 in diglyme with sodium methoxide. The two predominant bands

corresponded to 7-dehydro-cholesteryl-acetate 55 and 7-dehydro-

cholesterol 161. The NMR spectrum of the product shows no bands

indicative of the formation of a spiroheptatriene resulting from

addition of an intermediate to benzene.

Pyrolysis of 5-Cholesten-3β-ol-3-acetate-7-one p-Toluene-

sulfonylhydrazone 54 with Sodium Methoxide in Tetrachloroethylene.

A mixture of 0.500 g. (0.0008 mole) of 5-cholesten-3β-ol-3-acetate-

7-one tosylhydrazone and 3.5 ml. of 0.46 N sodium methoxide

(0.0016 mole) was used in the usual manner to form the sodium salt

of the tosylhydrazone.

Tetrachloroethylene, 200 ml., was added to the sodium salt and

heated under reflux until nitrogen evolution ceased. Work up in the

usual manner gave 0.323 g. of a brown oil. Thin layer chromatog-

raphy of this material showed five bands of which two were

predominant. This thin layer chromatogram was identical to that from the pyrolysis of 54 in diglyme and in benzene with sodium methoxide.

5,16-Pregnadiene-3β-ol-20-one p-Toluenesulfonylhydrazone

167. To a solution of 7.8 g. (0.041 mole) of p-toluenesulfonyl-hydrazine in ca. 500 ml. of methanol was added 13.0 g. (0.041 mole) of 16-dehydropregnenolone. After the resulting solution had been stirred overnight at room temperature, the methanol was removed in vacuo. Recrystallization of the crude product from chloroform-hexane afforded 17.1 g. of yellow solid, m.p. 160-166° (dec.). Recrystallization from acetone gave the a white solid, m.p. 173-175° (dec.), $a]_D$ -18.4°.

Anal. Calcd. for: $C_{28}H_{38}N_2SO_3$: C, 69.67; H, 7.94

Found: C, 69.67; H, 7.44.

The ultraviolet spectrum shows maxima of 258 mμ, ϵ = 14,500 and 226 mμ, ϵ = 14,600. The infrared spectrum displays bands at 1590 cm^{-1}, 1340 cm^{-1}, 1160 cm^{-1} and 810 cm^{-1}.

Pyrolysis of 5,16-Pregnadiene-3β-ol-20-one p-Toluene-sulfonylhydrazone 167 with Sodium Methoxide in Glyme. A mixture of 16-dehydro-5-pregnene-3β-ol-20-one 2.00 g. (0.0042 mole) and 18.2 ml. of 0.46 N sodium methoxide (0.0084 mole) was used in the usual manner to form the sodium salt of the tosylhydrazone. Anhydrous

glyme, ca. 200 ml., was added to the sodium salt and the solution was heated at reflux for 4 hours. The white precipitate was removed by filtration, and the glyme was then removed in vacuo from the filtrate. The residual yellow solid was dissolved in 200 ml. of chloroform, washed with water and dried over magnesium sulfate. - Removal of the chloroform in vacuo gave 1.480 g. of yellow solid. Thin layer chromatography indicated four components, one of which was predominant (R_f 0.19; benzene-ethyl acetate, 3:1). Chromatography of this mixture on 30 g. of acid-washed alumina gave 0.651 g. (43%) of a yellow oil (200 ml. of ether). Thin layer chromatography showed this material was a mixture of five components and this fraction was discarded.

Elution with 200 ml. of methanol gave 0.860 g. (57%) of a white solid, m.p. 205-250° (dec.) [lit. (90), m.p. > 300°].

The ultraviolet spectrum shows a maximum at 226 mμ, ε = 4,100. The infrared spectrum displays bands at 3250 cm^{-1} and 1590 cm^{-1}. The NMR spectrum shows sharp bands at 64.5 c.p.s. (19-Me) and 58.5 c.p.s. (18-Me), a methyl on a double band at 2.23δ and broad bands centered at 5.4δ (1H) and 6.78δ (1H) consistent with [16-17-C]-(5-methyl)-pyrazolandrost-5-ene-3β-ol 169.

Acetylation of the alcohol gave 0.620 g. of white solid, m.p. 194-197°. Recrystallization from acetone gave the analytical sample, m.p. 196-198°, a]$_D$ -81°.

<u>Anal</u>. Calcd. for $C_{25}H_{34}N_2O_3$: C, 73.14; H, 8.35; N, 6.82

Found: C, 73.01; H, 8.39; N, 6.86

The ultraviolet spectrum shows a maximum at 242 mμ, ϵ = 8,960. The infrared spectrum displays significant bands at 1725 cm^{-1} and 1590 cm^{-1}. The NMR spectrum shows two sharp bands at 61 c.p.s. (19-Me) and 69 c.p.s. (18-Me), and sharp bands at 2.08 δ due to an acetate methyl, 2.27 δ due to a methyl on a double bond, and 2.68 δ attributable to an N-acetate methyl. This data is consistent with [16,17-C] (1'-acetate-5'-methyl) pyrazolandrost-5-ene-3β-ol-3-acetate.

<u>Photolysis of 5,16-Pregnadiene-3β-ol-3-acetate-20-one p-Toluenesulfonylhydrazone 167 with Sodium Methoxide</u>. To 100 ml. of anhydrous methanol was added 0.292 g. (0.013 mole) of clean sodium followed by 6.124 g. (0.013 mole) of 16-dehydro-5-pregnene-3β-ol-3-acetate-20-one tosylhydrazone 167. After the solution had been stirred for ca. 20 minutes, the methanol was evaporated <u>in vacuo</u>. The residual salt was broken up and dried overnight at 0.05 mm. The dry sodium salt was placed in 1200 ml. of tetrahydrofuran and irradiated under nitrogen. After 8.5 hours, the solvent was evaporated <u>in vacuo</u> to ca. 200 ml., poured into 1.5 l. of water and extracted with chloroform. The organic layers were washed with 5% hydrochloric acid and water, and dried over magnesium sulfate. Removal of the solvent <u>in vacuo</u> provided 3.680 g. of brown oil.

Thin layer chromatography indicated the presence of five products with the most polar product having the greatest intensity (R_f 0.54, ethyl acetate-methanol, 3:1). Chromatography of the reaction mixture on 60 g. of acid-washed alumina gave 1.310 g. (40%) of inseparable mixtures, 0.61 g. (19%) of an acetate (ether), and 1.320 g. (41%) of an acetate and an alcohol (methanol). Combination of the acetate and alcohol fractions, followed by acetylation gave 1.882 g. of a brown solid. Thin layer chromatography of this material indicated one product (R_f 0.50, benzene). Recrystallization from acetone gave a white solid, m.p. 194-198°. This compound was shown to be [16,17-C] (1'-acetate-5'-methyl) pyrazolandrost-5-ene-3β-ol-3-acetate by comparison of its physical properties with those of the compound prepared from the pyrolysis of 167.

16-Methyl-5,16-pregnadiene-3β-ol-3-acetate-20-one p-Toluene-sulfonylhydrazone 173. Tosylhydrazine, 2.8 g. (0.0150 mole), 16-methyl-16-dehydro-5-pregnene-3β-ol-3-acetate-20-one, 5.0 g. (0.0135 mole), and 280 ml. of methanol were heated under reflux for 3 hours. Concentration of the solution to ca. 175 ml. and cooling to room temperature afforded 4.5 g. of white needles, m.p. 188-191° (dec.), α]$_D$ -87°.

Anal. Calcd. for $C_{31}H_{42}N_2SO_4$: C, 69.11, H, 7.86

Found: C, 69.10, H, 7.94

Concentration of the mother liquors afforded 2.61 g. of needles, m.p. 184-188°.

The infrared spectrum of both crops of crystals showed strong bands at 3200 cm^{-1} and 1160 cm^{-1}.

Pyrolysis of 16-Methyl-5,16-pregnadiene-3β-ol-3-acetate-20-one p-Toluenesulfonylhydrazone 173 with Sodium Hydride in Glyme.

A solution of 100 ml. of glyme, 1.00 g. (0.0019 mole) of 16-methyl-16-dehydro-5-pregnene-3β-ol-3-acetate-20-one tosylhydrazone and 0.25 g. (0.010 mole) of sodium hydride were heated under reflux for 4 hours. The white precipitate of sodium sulfinate and excess sodium hydride were removed by gravity filtration. The glyme was then removed in vacuo from the filtrate affording 0.668 g. of a pink oil which quickly solidified. This oily solid was washed with 10 ml. of cold hexane leaving behind 0.324 g. (47%) of white solid, m.p. 158-163° (dec.). Recrystallization from hexane afforded 0.298 g. of compact needles, m.p. 162-164° (dec.), α]$_D$ -87°.

Anal. Calcd. for C$_{24}$H$_{34}$N$_2$O$_2$: C, 75.35; H, 8.96; N, 7.32

Found: C, 75.56; H, 9.08; N, 7.04

The infrared spectrum shows a strong band at 1648 cm^{-1}.

The ultraviolet spectrum shows a maximum at 252 mμ, ε = 7,300 (methanol). The NMR spectrum shows broad bands at 5.40δ (1H) and 4.50δ (1H) and sharp bands at 2.18δ (21-Me), 2.01δ (acetate methyl group), 1.95δ (methyl group at C-16), 63 c.p.s. (19-Me) and

57 c.p.s. (18-Me). This data is consistent with [16,17-C] (3',5'-dimethyl) pyrazolenineandrost-5-ene-3β-ol-3-acetate 175.

[16,17-C] [2 -Acetate-3',5'-dimethyl] pyrazolineandrost-5-ene-3β-ol-3-acetate-17-ol 174. A mixture of 0.200 g. of steroidal pyrazolenine 175, 1 pellet of sodium hydroxide, 15 ml. of methanol and 5 ml. of water were heated on a steam bath for ca. 20 minutes. Removal of the solvent in vacuo, followed by drying in a vacuum dessiccator with phosphorous pentoxide as a dessiccant, afforded an orange solid. Acetylation of this material in the usual manner gave 0.164 g. of a dark brown oil. Trituration with methanol followed by recrystallization from acetone gave 0.091 g. of white needles, m.p. 227-228.5°, a]$_D$ -130°.

Anal. Calcd. for $C_{26}H_{38}N_2O_4$: C, 70.56; H, 8.65; N, 6.33

Found: C, 70.61; H, 8.78; N, 6.32

The ultraviolet spectrum shows a maximum at 242 mμ, ε = 9000 (methanol). The infrared spectrum shows a broad band at 3400 cm^{-1} and strong bands at 1725 cm^{-1} and 1640 cm^{-1}. The NMR spectrum displays a broad band at 5.34δ (1H) due to the C-6 olefinic proton, a broad band at 4.55δ (1H) due to the 3α-proton, a sharp band at 3.32δ (1H) attributable to a proton on an oxygen, a sharp band at 2.19δ (3H) attributable to a methyl group on the carbon atom of a carbon-nitrogen double bond, sharp bands at 2.02δ and 2.00δ due to an N-acetate and an O-acetate, a sharp band at 1.48δ due to the

methyl on C-16, and sharp bands at 61 c.p.s. (19-Me) and 56 c.p.s. (18-Me). The sharp band at 3.32δ disappears after the NMR sample is shaken with deuterium oxide.

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