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Title STEROID-DIHALOCARBENE REACTIONS

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Dihalocarbenes have been generated by thermal decomposition of sodium trichloroacetate and tribromomethylphenylmercury, and give mono dihalocyclopropyl adducts with steroid dienes. Such compounds offer an easy starting point for the synthesis of unusual derivatives of potential biological interest. Under the same conditions, however, addition to non-conjugated double bonds does not take place. This lack of reactivity can be ascribed to several factors, none of which is totally satisfactory. Deoxidation of allylic alcohols has also been observed under carbene conditions, and a similar new reaction of allylic acetates was discovered.

STEROID-DIHALOCARBENE REACTIONS

by

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STEROID-DIHALOCARBENE REACTIONS

INTRODUCTION

The reactions of intermediates containing carbon in an abnormal valence state have long been a fertile field of investigation for the organic chemist. The chemistry of carbonium ions, carbanions and free radicals, species in which the trivalent carbon bears a positive charge, a negative charge, and no charge but a free electron respectively, have been studied extensively. Only recently, with the advent of modern techniques has a fourth type of intermediate, the carbene, been shown to exist. Postulated in 1862 (15), carbenes

were not conclusively accepted until 1950 when Hine (20) proved their existence in the basic hydrolysis of haloforms. Since that time numerous studies have broadened our understanding of the physical and chemical properties of these intermediates.

Carbenes have been shown to exist in both the singlet state with the two free electrons paired, and in the triplet state with two unpaired electrons (19, p. 291-317). Carbenes generated in solution are usually in the singlet state and react in this form before decay to the more stable triplet state. The two common ways of generating

methylene, $:CH_2$, the parent member of the carbene family, are the photolysis or thermal decomposition of diazomethane or ketene.

$$CH_2N_2 \xleftrightarrow[\text{or } \Delta]{h\nu} :CH_2 + N_2 \quad (6)$$

$$CH_2 = C = O \xrightarrow[\text{or } \Delta]{h\nu} :CH_2 + CO \quad (29)$$

The reactions of methylene are not of great synthetic interest because of the large variety of products that arise from competition between insertion and addition reactions (6, 8, 39). However, so called carbene complexes, such as the Simmons-Smith reagent (36), are used quite extensively to add methylene to olefins with no observation of insertion products. Considerable reference has been made to carbene transfer reagents but the question of free carbene or carbene transfer has not been completely solved. Miller (25) has observed that trichloromethyllithium, formerly believed to be a carbene precursor, is a stable electrophilic species at -100°, which reacts with olefins to form the cyclopropyl adduct without the formation of a carbene intermediate. On the other hand, Seyferth (34) has presented data which indicate dichlorocarbene, generated by the thermal decomposition of sodium trichloroacetate or bromodichloromethylphenylmercury, is a free carbene. Other methods for generating dihalocarbenes are illustrated by the following equations.

$CHCl_3 + KOtbu \longrightarrow :CCl_2 + KCl + t\text{-}buOH$ (7)

$Cl_3CCOOEt + NaOMe \longrightarrow :CCl_2 + NaCl + OC(OMe)(OEt)$ (28)

$CCl_4 + LiC_4H_9 \longrightarrow :CCl_2 + LiCl + C_4H_9Cl$ (24)

$Cl_3CCOCCl_3 + 2RO^- \longrightarrow 2{:}CCl_2 + (RO)_2CO + 2Cl^-$ (16, 21)

$C_6H_5HgCBr_3 \xrightarrow{\Delta} :CBr_2 + C_6H_5HgBr$ (33)

$Cl_3CCOONa \xrightarrow{\Delta} :CCl_2 + NaCl + CO_2$ (38)

The last two equations illustrate methods of generating a carbene under essentially neutral conditions. Wagner (38) has shown that the thermal decomposition of sodium trichloroacetate will give dichlorocarbene if the acidity of the solvent is such that the reverse of reaction (1) is practically impossible. If the solvent is acidic, the

$$CHCl_3 + B^- \rightleftharpoons CCl_3^- + BH \qquad (1)$$

$$CCl_3^- \rightleftharpoons :CCl_2 + Cl^- \qquad (2)$$

reverse of reaction (1) occurs and the formation of the dichlorocarbene is prohibited.

Using 1, 2-dimethyoxyethane as the solvent, Wagner has obtained good yields of the dichlorocyclopropyl adducts of simple olefins. He has also observed that the more nucleophilic olefin will give the higher yield of addition compound, and furthermore that the yield of the adduct was higher when the olefin was in excess. The yield of adduct was shown to increase on increasing the olefin to solvent

ratio. These data confirm the highly reactive, electrophilic nature of the carbene intermediate.

This method for generating dichlorocarbene has the advantage of being applicable to base sensitive olefins. The procedure eliminates competition of the electrophilic carbene with the nucleophilic alcohol or alkoxy anion present in other methods of generation. It is also one of the few methods for obtaining good yields of the cyclopropyl adduct when the olefin is not used as the solvent.

Seyferth (33) has developed a procedure which also avoids basic conditions and gives rather high yields of the dihalocyclopropane. Thermal decomposition of trihalomethylphenylmercury compounds appears to be a good method for generating dichloro-, dibromo-, and bromochlorocarbene (eq. 3). This method is quite

$$C_6H_5HgCX_3 \xrightarrow{\Delta} C_6H_5HgX + :CX_2 \qquad (3)$$

useful in reactions with olefins of low reactivity. Ethylene, which will not react with dichlorocarbene generated by the classic potassium tert-butoxide/chloroform procedure was observed to yield 1, 1-dichlorocyclopropane in 65 percent yield (35). One can also reconvert the phenylmercuric bromide, which precipitates during the reaction, into the carbene precursor. Whereas in Wagner's method there is the nucleophilic trichloroacetate ion to react competitively with the carbene, this is not the case in Seyferth's method.

It was of interest to investigate the possibility of adding dihalocarbene to steroids. If addition would occur one would have a simple one-step synthesis of small ring steroid compounds. At the present time there are only a limited number of available reaction sequences which introduce a cyclopropane ring into the steroid nucleus (2, 14, 17, 32). If the carbene method would supply a convenient synthesis of small ring steroids it would make a study of these potentially biologically and chemically interesting compounds more practical. Another interesting aspect of dihalocarbene addition is the effect on biological activity which the addition of halogen is known to have. Fried and Sabo found that introduction of a 9α-chlorine or fluorine atom had a remarkable effect on the biological activity of cortical hormones (12, 13, 18). Since that discovery a number of attempts have been made to introduce halogens in other positions on the steroid molecule (10, p. 135-136). The addition of dihalocarbenes to steroids might give biologically interesting compounds, or these derivatives might easily be converted into a whole series of halogenated products via standard reactions.

The stereochemistry of addition and the effects of steric hindrance would also be an interesting aspect of such a study. The steroid nucleus offers an ideal framework within which to study the stereochemistry of many reactions, because of the rigid ring structure. One could determine if the carbene attacks from the α or

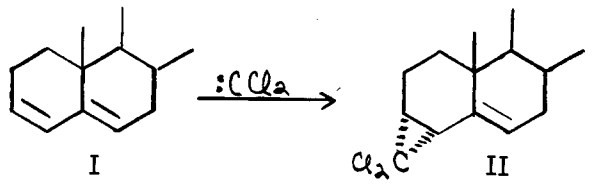
β face of the molecule, or both, and also obtain data on what steric effects the C-18 and C-19 angular methyl groups exert on the addition. By use of available steroids containing various degrees of unsaturation one could also test the possibility of selective carbene addition.

It was also felt important to develop synthetic methods in which the olefin was not present in large excess as solvent. Such a procedure is obviously necessary with solid compounds and would be useful for more expensive olefins of other types.

Because of the common functional groups present on steroids, it was also felt that this study would reveal which of these groups were compatible with the various conditions for generating carbenes. Compounds containing a carbonyl group were not considered because of the known nucleophilic attack of the trihalomethyl anion upon ketones. Also the use of compounds containing an alcohol group presents the problem of competition between attack on the carbon-carbon double bond and on the ρ electrons of the oxygen atom. Attack on the oxygen gives rise to deoxidation products and a number of carbene reactions with alcohols (eq. 4) giving rise to these products appear in the literature (31, 37). However, no such products have previously been reported when acetates are used to protect the alcohol group. Protective groups for ketones are also available.

$$ROH + :CX_2 \longrightarrow R^+ + CO + X^- + HX \qquad (4)$$

Since the inception of this work a number of articles concerning carbenes have appeared in the literature. Several of these articles deal with carbene addition to steroids. Workers in the Syntex laboratories (22) have reported various carbene additions to steroids and have found that dihalocarbenes will add to a 3, 5-diene system (I), with exclusive attack on the 3-4 carbon-carbon double bond (II) when a C-19 methyl group is present in the molecule (eq. 5).



I II (5)

Their explanation for this was that in order for the carbene to add to the 5-6 double bond, the vacant orbital of the carbene must overlap the π-orbital of the olefin. In order for this orientation to be maintained one of the halogens of the carbene is projected toward the C-19 methyl group, thus sterically inhibiting addition. This does not explain, however, why α attack did not occur. Using the smaller difluorocarbene they have successfully added to the 5-6 carbon-carbon double bond (III) (eq. 6). For this addition they reported the sur-

I III (6)

prising feature of β (top side) attack. While this is not without precedance, e. g. nitration (3), most reagents attack steroids, especially ring B, from the α side (9, p. 14). To support β-attack they have

comparative molecular rotations with similar compounds, such as the isomeric epoxides. Nuclear magnetic resonance spectra of the difluorocarbene adduct showed splitting of the C-19 methyl group. If one accepts the hypothesis that cis stereochemistry is a prerequisite for such a splitting, this data also supports the β adduct structure.

Cookson (5) has successfully added dibromocarbene to the 2-3 double bond of three steroids. It is of interest to note that he did not determine the stereochemistry of addition but assumed the adduct to be α, using the reasoning that α is the normal mode of attack on steroids. Müller (26) has successfully added methylene, although in low yields, to some steroids containing an aromatic ring A.

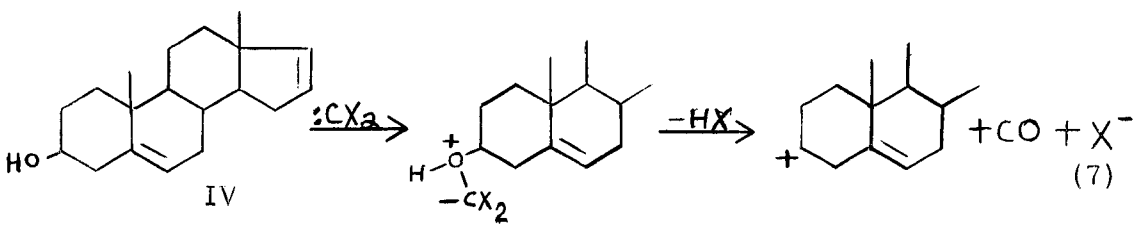
It was the purpose of this investigation to determine whether conditions could be found for the addition of carbenes to various steroid olefins. In particular it was hoped that the general non-reactivity of steroids reported by the Syntex group (22) might be traced to their method of carbene generation. In case of failure of carbene addition it was hoped that reasonable explanations could be found; in case of addition it was hoped that definite stereochemical assignments could be made to the products.

DISCUSSION

Our initial experiments were aimed at generating dihalocarbenes by various new procedures in the hope that it might be possible to effect addition to the 5, 6 double bond of cholesterol or cholesteryl acetate. Syntex workers (22), using sodium trichloroacetate in diglyme were unsuccessful in their attempts to add to a similarly situated olefin; therefore, our initial attempts were to add dibromocarbene, by the bromoform/potassium tert-butoxide procedure (7), or by the thermal decomposition of tribromomethylphenylmercury (33).

It was believed that the nucleophilicity of the trisubstituted double bond of cholesteryl acetate should be such that attack of the electrophilic carbene would occur. A possible reason for the previously observed failure in the sodium trichloroacetate case was competition between the nucelophilic trichloroacetate anion and the olefin for the carbene. Using tribromomethylphenylmercury, as the carbene precursor, the presence of a nucleophilic species in the reaction is limited to the olefin. When the experiments were run, however, it was observed that only unreacted starting material was recovered. This confirms the observation that the 5, 6 double bond of steroids containing a C-19 methyl group is unreactive in the presence of dihalocarbenes other than difluorocarbene.

The addition of dihalocarbene to another position of the molecule was also attempted. 5, 16-androstadiene-3β-ol (IV) was synthesized by Barton's procedure (1) and subjected to conditions under which dichlorocarbene was generated. Thin layer chromatography of the crude reaction product showed at least seven products. The polarity of the major components indicated that the course of the reaction probably proceeded through a deoxidation step (eq. 7) rather than addition. No attempt was made to separate the products

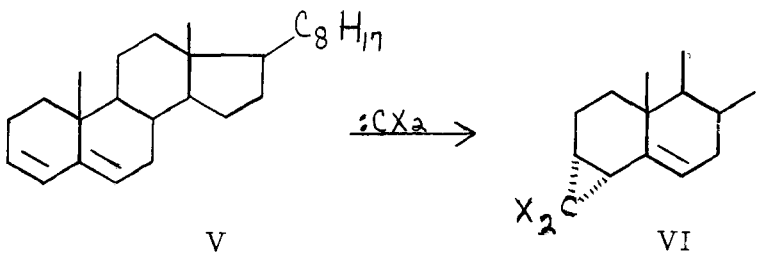


(7)

of this reaction. It was noted that no deoxidation products were observed in the case of cholesterol but a number of products arose from the carbene reaction with IV. A possible explanation for this is the difference in temperature at which the reactions were carried out. The bromoform/potassium tert-butoxide reaction was run at 0° and the decomposition of tribromomethylphenylmercury at 80°, in benzene. The thermal decomposition of sodium trichloroacetate was carried out in diglyme at 130°, and also involves the presence of a basic species which might favor deoxidation.

After these studies had shown that it was more difficult to add dihalocarbenes to steroid olefins than expected, it was felt

necessary to investigate our reaction conditions on a sterically less hindered system. Since it had been reported (22) that dichlorocarbene added to the 3, 4-double bond of 3, 5-androstadiene-17β-ol-acetate, we studied the analogous 3, 5-cholestadiene (V) system. Using both dichloro and dibromocarbene, generated thermally from sodium trichloroacetate and tribromomethylphenylmercury respectively, addition to give mono adducts (VIa and VIb) was successful. although the yields were only in the order of 30 percent. The ultraviolet spectra of these adducts show only end adsorption, indicating



V VI

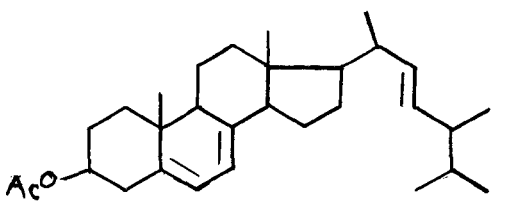
a) X = Cl
b) X = Br

that conjugation was no longer present in the molecule. Support of the mono-adduct is also shown by the presence of one vinyl hydrogen in the nuclear magnetic resonance spectra. The products are assigned the 3α, 4α structure, in analogy to the assignments made by Knox et al. (22) to similar adducts, though it should be re-emphasized that the stereochemistry assignments are tentative. Naturally the position of attack was indicated by the presence of

only one vinyl hydrogen in the nuclear magnetic resonance spectra of the products.

A brief survey was made in order to find the best possible conditions for these additions. As suspected, slow addition of the carbene percursor, especially in the case of sodium trichloroacetate, appears to be critical both in maintaining a high concentration of olefin relative to carbene, and in preventing reaction of the carbene with precursor. Since all of the dihalocarbenes can be generated by the Seyferth method (33), this would appear to be the most promising procedure for future study. Some difficulty, however, was encountered in separating product from phenylmercuric bromide, also formed in this reaction.

Ergosterol acetate (VII) was also investigated because it was thought that the side chain double bond should be relatively free from steric hindrance. Indeed dichloro and dibromocarbene added

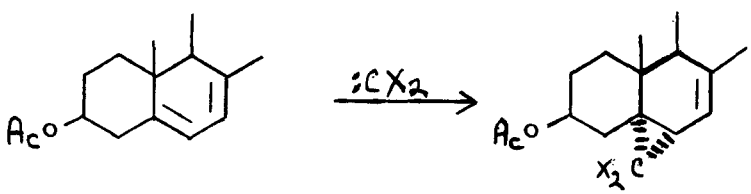


VII

cleanly to give a mono-adduct. The ultraviolet spectra of these compounds indicated the surprising result that addition had occurred to the conjugated system. This was confirmed by the presence of the typical trans double bond peak in the infrared spectra at 968 cm^{-1}.

The nuclear magnetic resonance spectrum of the adduct, especially the alcohol from saponification, shows three vinyl hydrogens, indicating that addition had occurred in ring B. If addition had occurred to the side chain double bond then only two vinyl hydrogens would have been present in the product. An explanation for the non-reactivity of the side chain double bond, in the presence of excess dihalocarbene, is not immediately obvious.

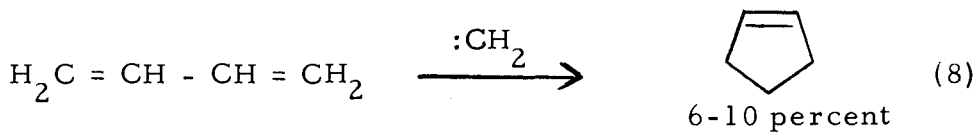
While the Syntex workers (22) favored β attack at the 5, 6 double bond, in the case of the difluorocarbene adduct and with 19-nor-steroids, they by no means proved this and failed to explain why the typical nature (i.e. α) of electrophilic attack at that position was not noted. Since we were able to add the very bulky dibromocarbene with no more difficulty than dichlorocarbene we tentatively favor α attack in the ergosterol acetate (VII) system. That attack in both cases was from the same side is indicated by the nuclear magnetic resonance spectra of the two products, VIIIa and VIIIb, which are quite similar.



VII VIII

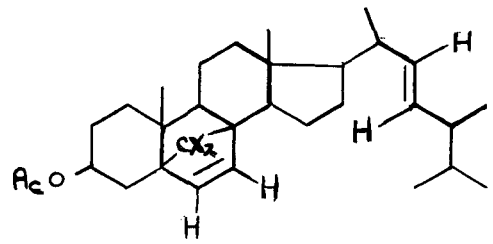
a) X = Cl
b) X = Br

One now has to explain why addition occurs at the 5, 6 position in ergosterol acetate (VII) but not in cholesterol or cholesteryl acetate. One possibility is that the diene system causes enough flattening of the ring to prevent steric inhibition by the angular methyl group. Another possibility is raised by the fact that in both our work and that of Knox et al. (22), addition of dihalocarbene other than difluorocarbene occurs in the presence of a 19-methyl group only with conjugated dienes. One of the classic pieces of evidence for the singlet character of dihalocarbenes is that the reactivity toward it of isolated olefins and conjugated systems is of the same order of magnitude. Were the reacting species a triplet (diradical) attack to give the conjugated radical intermediate would be favored. Possibly the reacting species under our conditions was triplet dihalomethylene though additional evidence for this postulate would be necessary. Franzen (11) has recently reported that he observed 1:4-addition of methylene to butadiene (eq. 8), implying some triplet reactivity. On the other hand, Ledewith (23) and Orchin (27)



(8)

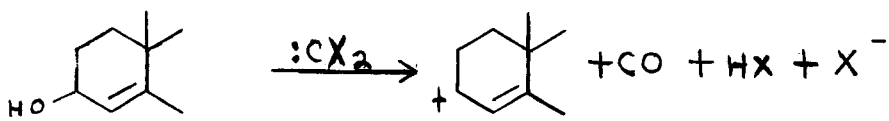
have reported that they observed only 1:2-addition of carbenes with conjugated dienes. They found no evidence for 1:4-addition. We can rule out 1:4-addition in our case, as the product (IX) would have four vinyl hydrogens. Nevertheless, a triplet species would



IX

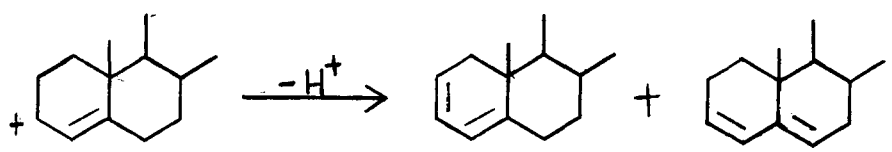
be expected to add more readily to a conjugated diene than an isolated olefin, in this case by a two step process.

With successful addition to 3, 5-cholestadiene (V) and ergosterol acetate (VII), investigation was directed toward the 4-ene system. The reaction of 4-cholestene-3β-ol (X) with both dichloro and dibromocarbene led to facile deoxidation under conditions where 5-ene-3-ol systems were stable. This indicates, as expected, that deoxidation to an allylic carbonium ion (XI) is energetically quite favorable. It is interesting to note that this



X XI

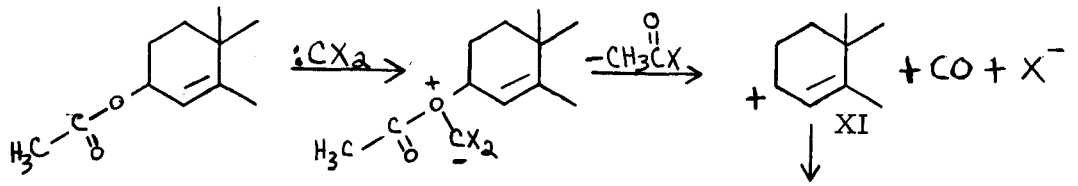
reaction, carried out in an aprotic solvent gives a mixture of 2, 4-(XII) and 3, 5-diene (V), whereas the usual carbonium ion,



XI XII V

formed in acid media, gives only V (9, p. 263). Presumably acid converts XII to V.

Since an allylic alcohol was readily deoxidized, a study was made of the corresponding 4-ene-3β acetate XIII. Suprisingly, however, the major product from reaction of XIII with thermally generated dichloro and dibromocarbene was V, resulting from deacetoxidation. A reaction analogous to that of alcohol deoxidation appears to have occurred. The mechanism shown below seems



XIII

V

reasonable enough but fails to explain why only V is formed, and no XII.

CONCLUSIONS

It has been shown that the method of carbene generation is not the cause of the surprising non-reactivity of steroid olefins toward dihalocarbenes. This is particularly surprising in view of the recent demonstration (34) that the methods employed involved free carbenes and not dihalomethylene transfer reagents. In the case of 5, 6 olefins, one is forced to the conclusion that stereo-electronically, carbene attack can only occur from the β side of the molecule and that the steric shielding of the C-19 methyl group is sufficient to prevent such a reaction. Additional studies are necessary to determine the fate of the dihalocarbenes which do not add to the steroid.

In contrast to such lack of reactivity was the observation of mono-addition of dihalocarbenes to conjugated dienes. Especially in the case of addition to ring B of ergosterol acetate, one is forced to the conclusion that the factors which prohibit attack in the cholesterol case cannot be operating here. Failure to add to the side chain double bond in ergosterol acetate was also surprising. Reaction of dihalocarbenes with even more hindered diene systems is obviously the next subject to investigate. It should also prove relatively simple to develop this new reaction into a synthetically useful route to ring B substituted derivatives.

With one exception, isolated steroidal alcohols have been found to be relatively non-susceptible to deoxidation reactions and may be used without protection. It has also been found, however, that allylic alcohols, which give dienes via this reaction cannot be protected as the acetate. This interesting reaction has heretofore not been observed.

In summary then, the hoped for general route to small ring steroids has not been realized. Specific cases have been discovered, however, and promise to provide a useful starting point for such a synthesis, as well as to provide some interesting information on the nature of carbene addition reactions.

EXPERIMENTAL

All melting points were recorded on a Büchii melting point apparatus and are corrected. Proton n. m. r. spectra were run in carbon tetrachloride or deutero chloroform and are reported as parts per million from internal tetramethylsilane. Optical rotations were run on ca. one percent solution in chloroform. Infrared absorption spectra were determined using a Beckman IR-8 spectrometer. Ultraviolet absorption spectra were measured in hexane with a Beckman Model DB recording spectrometer. "Worked up in the usual manner" refers to washing with saturated salt solution, five percent sodium bicarbonate, five percent hydrochloric acid, saturated salt solution, water, and drying over sodium sulfate. All chromatographies were run using activity III acid washed Merck alumina.

Tribromomethylphenylmercury. --Into a dry 3-l. three necked flask, equipped with an efficient stirrer, under an atmosphere of dry nitrogen, was placed 89. 4 g. (0. 25 mole) of phenylmercuric bromide, 252. 8 g. (1. 0 mole) of freshly distilled bromoform, and 1. 2 l. of benzene (freshly dried by distillation). Solid potassium tert-butoxide [from 19. 5 g. (0. 5 g. atom) of potassium] was added with vigorous stirring and cooling (ice bath) over a 35 minute period. The reaction mixture was stirred for an additional hour at 0°, and

then poured into 1.5 l. of distilled water.

After 1.5 hours, at room temperature, the mixture was filtered and the residue washed with 60 ml. of warm benzene. Subsequent drying of this residue in vacuo afforded 15.4 g. (17 percent recovery) of phenylmercuric bromide, m.p. 282-285°. The aqueous phase of the filtrate was extracted with two 250 ml. portions of benzene. These extracts, combined with the original benzene phase, were dried over sodium sulfate, and then concentrated in vacuo at 25°. There remained 67.1 g. (49.7 percent) of a cream white solid, m.p. 81-97°. Rapid recrystallization from a mixture of 250 ml. of n-hexane and 75 ml. of chloroform at 50° yielded 19.4 g. of a light yellow solid. Reduction of the mother liquor in vacuo to approximately one-third the original volume afforded 10.9 g. of a yellow solid. The total yield was 30.3 g. (23.3 percent), m.p. 114-116° (dec.), [lit. (35, p. 1164) m.p. 119-120°].

The reported yield (30, p. 730) following this procedure was approximately 40 percent. It was noted at the end of this experiment that the stirring shaft had sheared during the reaction and it is believed that this is the reason for the low yield.

Attempted Addition of Dibromocarbene to Cholesteryl Acetate. --A mixture of 3.14 g. (0.007 mole) of cholesteryl acetate and 10.8 g. (0.022 mole) of tribromomethylphenylmercury in 15 ml.

of dry benzene was heated under reflux for six hours. The solution was filtered and the filtrate worked up in the usual manner. Concentration of the organic layer in vacuo afforded 7.1 g. of a yellow gum. Chromatography of this material gave 2.9 g. (93.5 percent recovery) of cholesteryl acetate, m.p. 112-115°, fractions 16 through 25 (hexane-benzene, 1:1). Further elution with benzene afforded 3.6 g. of a white solid, m.p. 280-284° (phenylmercuric bromide).

Identical results were obtained when dichlorocarbene was generated in the presence of cholesteryl acetate in diglyme. Ninety-one percent recovery of cholesteryl acetate was obtained.

Thin layer chromatography of the crude product, benzene-ethyl acetate (9:1), showed only one compound present. The Rf value, 0.619, was identical to that of cholesteryl acetate.

3β-Hydroxyandrost-5-en-17-one Hydrazone. -- A mixture of 15 g. (0.045 mole) of 3β-acetoxyandrost-5-en-17-one in 88.5 ml. of absolute ethanol, 22 ml. of triethylamine (dried by distillation from activity I alumina), and 64 ml. of 64 percent hydrazine was heated under reflux for 1.25 hours. The mixture was poured into water and extracted with ether three times. The combined ether extracts were worked up in the usual manner. Concentration of the ether in vacuo afforded 12.1 g. of a white solid, m.p. 197-205°. Recrystallization of the hydrazone from ethanol-water afforded 11.5 g. (80.7 percent)

of a white solid, m.p. 210-215° [lit. (1, p. 475) m.p. 287°].

The discrepancy in the melting point could not be explained, but using this compound in the reaction sequence gave the correct final product.

17-Iodo-5, 16-androstadiene-3β-ol. -- To 11.5 g. (0.038 mole) of 3β-hydroxyandrost-5-en-17-one hydrazone in 200 ml. of tetrahydrofuran and 25 ml. of triethylamine was added 15.0 g. (0.059 mole) of iodine. The reaction vessel was cooled by a water bath during the addition of the iodine and the mixture was stirred vigorously, under an atmosphere of nitrogen. When the addition of iodine was complete the stirring was stopped. The precipitate was removed by filtration and washed with cold methanol. Recrystallization from ethanol-water afforded 4.4 g. (28.3 percent) of a white solid, m.p. 172-174° [lit. (1, p. 475) m.p. 172-174°].

5, 16-Androstadiene-3β-ol. --A solution of 4.4 g. (0.011 mole) of 17-iodo-5, 16-androstadiene-3β-ol and 43.7 g. (1.9 mole) of sodium in 300 ml. of absolute ethanol was heated under reflux for two hours (until all the sodium had dissolved). The solvent was removed in vacuo to give 2.5 g. of a white solid, m.p. 121-130°. Chromatography on 60 g. of alumina afforded 2.2 g. of a white solid, m.p. 130-137°. Recrystallization of this material from methanol-water afforded 2.1 g. (70 percent) of a white solid, m.p. 137-139°

[lit. (1, p. 475) m.p. 140-141°].

Attempted Addition of Dichlorocarbene to 5, 16-Androstadiene-3β-ol. --A solution of 0.425 g. (0.002 mole) of 5, 16-androstadiene-3β-ol and 3.08 g. (0.016 mole) of sodium trichloroacetate was heated at 80° under an atmosphere of nitrogen for six hours. The solution was poured into 500 ml. of distilled water and extracted five times with ether. The combined ether extracts were worked up in the usual manner and concentration of the ether in vacuo afforded 1.1 g. of a brown oil. Thin layer chromatography, benzene-ethyl acetate (9:1), showed this material to be a mixture of at least seven products. No attempt was made to isolate these compounds, though their polarity suggested that deoxidation had been a major pathway.

3, 5-Cholestadiene. --A mixture of 10.0 g. (0.026 mole) of cholesterol and 20.0 g. (0.125 mole) of anhydrous cupric sulfate in 200 ml. of dry xylene was heated under reflux for 24 hours. At this time the solution was filtered, and the inorganic material washed with xylene. Removal of the xylene under reduced pressure afforded 8.25 g. of a glassy oil which solidified on standing. Chromatography on 160 g. of alumina afforded 7.83 g. of a white solid, (m.p. 63-70°), fractions 1 through 4 (hexane). Recrystallization of this material from ethanol gave 7.03 g. (73.3 percent) of white needles, m.p. 77.5-79.0° [lit. (9, p. 265) m.p. 80°].

3α, 4α-(Dichloromethylene)-5-cholestene. --To a solution of 5.0 g. (0.0135 mole) of 3, 5-cholestadiene in 100 ml. of dry diglyme was added 0.58 g. (0.003 mole) of sodium trichloroacetate, which had been dried at 60° and 20 mm. for 24 hours. This solution was stirred at 130° for 15 minutes in an atmosphere of nitrogen. At this time the mixture was cooled to below 100° and an additional 0.58 g. of sodium trichloroacetate was added. The mixture was again heated to 130°. This procedure was repeated at approximately 15 minute intervals until 7.87 g. (0.042 mole) of sodium trichloroacetate had been added. The solution was stirred at 130° for eight hours. The mixture was poured into 600 ml. of water and extracted five times with ether. The ether was washed five times with 50 ml. portions of water and worked up in the usual manner. Removal of the ether in vacuo afforded 5.2 g. of a dark tar. This material was chromatographed on 150 g. of alumina. Fractions 1 through 3 (hexane) afforded 3.24 g. of a white solid, m.p. 115-123°. Three recrystallizations of this material from chloroform-methanol afforded 1.79 g. (37.4 percent) of a white solid, m.p. 144.5-146°. $[\alpha]_D$ -33.5°.

Anal. Calc'd. for $C_{28}H_{44}Cl_2$: C, 74.47; H, 9.82; Cl, 15.71.
Found: C, 74.56; H, 9.89; Cl, 15.84.

Evaporation of the mother liquor gave 1.1 g. of a yellow oil, the ultraviolet spectrum of which showed λ_{max} 235, ε = 21,000.

Pure 3, 5-cholestadiene has λ_{max} 235, ε = 20, 000.

The infrared spectrum of 3α, 4α-(dichloromethylene)-5-cholestene showed significant bands at 1650 cm^{-1} (w), carbon-carbon double bond, and at 655 cm^{-1} (m) assigned to the C-Cl stretch.

The nuclear magnetic resonance spectrum showed one vinyl hydrogen as a multiplet at 5.8 p.p.m., and angular methyl bands at 0.67, 0.83, 0.90 and 0.92 p.p.m.

3α, 4α-(Dibromomethylene)-5-cholestene. --A solution of 0.31 g. (0.84 mmole) of 3, 5-cholestadiene and 0.43 g. (0.8 mmole) of tribromomethylphenylmercury in 50 ml. of dry benzene was heated under reflux, in an atmosphere of nitrogen, for 30 minutes. At this time the mixture was cooled and an additional 0.43 g. of tribromomethylphenylmercury was added. The solution was again heated under reflux for 30 minutes. This procedure was repeated at approximately 30 minute intervals until 3.52 g. (6.5 mmole) of tribromomethylphenylmercury had been added. The mixture was heated under reflux for four hours, cooled, and the mixture filtered. Concentration of the organic layer in vacuo afforded 1.26 g. of a yellow solid. The melting point, 173-240°, of this material suggested that most of it was phenylmercuric bromide. Chromatography of this material on 20 g. of alumina afforded 0.502 g. of a yellow gum, fractions 1 through 5 (hexane), which solidified on trituration

with methanol. On attempting to dissolve this material in chloroform it was noted that a white solid remained. Filtration of this material afforded 0.356 g. of a white solid, m.p. 280-284° (phenylmercuric bromide). Removal of the chloroform in vacuo afforded 0.140 g. of a yellow oil. Recrystallization of this material from chloroform-methanol gave 0.071 g. (24.2 percent) of a white solid, m.p. 139-141°.

Anal. Calc'd. for $C_{28}H_{44}Br_2$: C, 62.22; H, 8.20. Found: C, 62.56; H, 7.85.

The nuclear magnetic resonance spectrum showed one vinyl hydrogen as a multiplet at 5.78 p.p.m., and angular methyl groups at 0.67, 0.82, 0.88 and 0.91 p.p.m.

5α,6α-(Dichloromethylene)-ergost-7,22-diene-3β-acetate (Tentative Structure). --To a solution of 1.1 g. (2.5 mmole) of ergosterol acetate in 25 ml. of dry diglyme was added 0.52 g. (2.8 mmole) of sodium trichloroacetate. The solution was stirred in an atmosphere of nitrogen at 130° for 15 minutes. The mixture was cooled to below 100° and an additional 0.52 g. of sodium trichloroacetate was added. This procedure was repeated at 15 minute intervals until 3.7 g. (19.9 mmole) of sodium trichloroacetate had been added. The mixture was stirred at 130° for eight hours. The solution was poured into 500 ml. of water and extracted five times

with ether. The combined ether extracts were washed ten times with 50 ml. portions of water and worked up in the usual manner. The ether was removed in vacuo to give 1.29 g. of a brown oil. Chromatography on 32 g. of alumina gave 0.110 g. of an unidentifiable yellow oil, fractions 1 and 2 (hexane), possibly a deoxidation product although the ultraviolet spectrum did not show a 3, 5, 7-triene system. Fractions 12 through 17 (hexane-benzene, 4:1) gave 0.338 g. of a yellow oil. Trituration with methanol afforded 0.211 g. of a white solid. Recrystallization from chloroform methanol afforded 0.203 g. (15.3 percent) of a white solid, m.p. 149-151°. The ultraviolet spectrum of this compound showed only end adsorption.

Anal. Calc'd. for $C_{31}H_{46}O_2Cl_2$: C, 71.23; H, 8.90.
Found: C, 71.42; H, 9.08.

The infrared spectrum of this compound showed significant bands at 3010 cm^{-1} (w), vinyl hydrogen, 1645 cm^{-1} (w) assigned to the carbon-carbon double bond, 1725 cm^{-1} (s) carbonyl peak, and an acetate band at 1240 cm^{-1} (s). There was also a peak at 968 cm^{-1} (m) which was assigned to the trans double bond.

The nuclear magnetic resonance spectrum showed three vinyl hydrogens, as a multiplet, in the area 5.1 to 5.6 p.p.m., the C-3 hydrogen at approximately 4.85 p.p.m. and angular methyl peaks at 0.58, 0.78, 0.88, 0.97 and 1.15 p.p.m.

The sample used to determine the nuclear magnetic resonance

spectrum was saponified by heating under reflux for three hours in methanolic potassium hydroxide. Workup in the usual manner afforded a white solid. The nuclear magnetic resonance spectrum of this material helped to confirm that there were three vinyl hydrogens present in the molecule. No further data were obtained on this compound.

5α, 6α-(Dibromomethylene)-ergost-7, 22-diene-3β-acetate (Tentative Structure). --A mixture of 2.0 g. (0.004 mole) of ergosterol acetate and 6.98 g. (0.013 mole) of tribromomethylphenylmercury in 10 ml. of dry benzene was stirred under reflux in an atmosphere of nitrogen for six hours. The mixture was filtered and the precipitate washed with hexane. The combined organic layers were worked up in the usual manner and concentration of the organic layer afforded 3.87 g. of a dark tar. Chromatography of this material on 90 g. of alumina afforded 2.64 g. of a white solid, m.p. 111-122°, fractions 10 through 13 (hexane-benzene, 1:1). Recrystallization of this material from hexane-acetone afforded 0.238 g. of a white solid, m.p. 143-145°. The ultraviolet spectrum of this compound showed only end adsorption.

The infrared spectrum of this compound showed significant bands at 3010 cm^{-1} (w), assigned to the vinyl hydrogen, 1645 cm^{-1} (w), a shoulder band assigned to the carbon-carbon double bond,

1725 cm^{-1} (s) carbonyl, 1240 cm^{-1} (s) acetate band, and a peak at 965 cm^{-1} (m) assigned to the trans double bond.

The nuclear magnetic resonance spectrum showed three vinyl hydrogens, as a multiplet, in the area 5.1 to 5.7 p.p.m., the C-3 hydrogen at approximately 4.75 p.p.m. and angular methyl peaks at 0.57, 0.78, 0.87, 0.97 and 1.15 p.p.m.

4-Cholestene-3β-ol. --To a mixture of 20.0 g. (0.087 mole) of lithium tri-t-butoxyaluminohydride (4, p. 252) in 200 ml. of freshly distilled tetrahydrofuran was added 10.0 g. (0.026 mole) of 4-cholestene-3-one in 70 ml. of tetrahydrofuran. The mixture was stirred in an atmosphere of nitrogen for eight hours at room temperature. Excess lithium tri-t-butoxyaluminohydride was carefully decomposed with five percent acetic acid. The solution was extracted with ether and worked up in the usual manner. Removal of the ether in vacuo gave 6.71 g. of a white solid, m.p. 115-120°. Recrystallization from methanol-chloroform afforded 6.43 g. (64.0 percent) of a white solid, m.p. 129-131° [lit. (9, p. 260) m.p. 132°].

Attempted Addition of Dichlorocarbene to 4-cholestene-3β-acetate. --To a solution of 2.5 g. (0.006 mole) of 4-cholestene-3β-acetate in 25 ml. of dry diglyme was added 1.22 g. (0.006 mole) of sodium trichloroacetate. This solution was heated at 130° for 15 minutes. At this time the mixture was cooled to below 100° and an

additional 1.38 g. of sodium trichloroacetate was added. This procedure was repeated at approximately 15 minute intervals until 10.93 g. (0.06 mole) of sodium trichloroacetate had been added. This mixture was stirred for eight hours at 130°. The mixture was poured into 600 ml. of distilled water and extracted five times with ether. The combined ether extracts were worked up in the usual manner and removal of the ether in vacuo afforded 2.47 g. of a brown oil. Chromatography of this material on 90 g. of alumina afforded 1.66 g. (77.5 percent) of a yellow oil, fraction 1 (hexane), which solidified on trituration with methanol. Recrystallization of this material afforded 0.73 g. of a white solid, m.p. 71-74°. The ultraviolet spectrum of this material shows λ_{max} 235, ε = 21,700. Pure 3,5-cholestadiene has λ_{max} 235, ε = 20,000 (9, p. 16), m.p. 80°.

Attempted Addition of Dibromocarbene to 4-cholestene-3β-acetate. --To a mixture of 3.2 g. (0.005 mole) of 4-cholestene-3β-acetate in 10 ml. of dry benzene was added 10.1 g. (0.019 mole) of tribromomethylphenylmercury. The mixture was heated under reflux, in an atmosphere of nitrogen for eight hours. The solution was filtered and the precipitate was washed with 25 ml. of benzene. The combined benzene fractions were worked up in the usual manner. Concentration of the benzene in vacuo afforded 3.08 g. of a brown

tar. Chromatography of this material on 90 g. of alumina afforded 1.38 g. of a yellow oil, fractions 1 through 4 (hexane) which solidified on trituration with methanol. Recrystallization of this material from chloroform-methanol afforded 1.03 g. of a white solid, m.p. 75-79°. The ultraviolet spectrum shows λ_{max} 235, ε = 22,000. 3,5-cholestadiene has λ_{max} 235, ε = 20,000, m.p. 80°. Fractions 12 through 14 (benzene) gave 0.32 g. of a yellow oil. The nuclear magnetic resonance spectrum of this material showed no vinyl hydrogens. This material was thought to possibly be the dibromocarbene adduct but was not investigated further.

Attempted Addition of Dichlorocarbene to 4-cholestene-3β-ol. --To a mixture of 5.0 g. (0.013 mole) of 4-cholestene-3β-ol in 100 ml. of diglyme was added 1.04 g. (0.006 mole) of sodium trichloroacetate. The solution was heated at 130° in an atmosphere of nitrogen, for 15 minutes, and then cooled to below 100°. An additional 1.02 g. of sodium trichloroacetate was added. This procedure was repeated until 8.32 g. (0.045 mole) had been added. The mixture was stirred at 130° for eight hours. The solution was poured into 600 ml. of distilled water and extracted five times with hexane. The combined hexane extracts were worked up in the usual manner. Removal of the hexane in vacuo afforded 5.86 g. of a dark oil. Thin layer chromatography of this material indicated at least eight

products. This material was chromatographed on 90 g. of alumina. Fractions 2 through 4 (hexane), afforded 2.71 g. of a yellow oil, the ultraviolet spectrum of which shows λ_{max} 235, ε = 12,700; λ_{max} 266, ε = 2,590; indicating a composition of 1.0 g. of 2,4-cholestadiene and 1.7 g. of 3,5-cholestadiene. No attempt to isolate the other components was made. Elution of the column with methanol afforded 2.5 g. of a brown gum.

BIBLIOGRAPHY

1. Barton, D. H. R., R. E. O'Brien and S. Sternhell. A new reaction of hydrazones. Journal of the Chemical Society, 1962, p. 470-476.

2. Barton, D. H. R. and J. M. Beaton. A synthesis of aldosterone acetate. Journal of the American Chemical Society 83:4083-4089. 1961.

3. Bowers, A., María Blanca Sánchez and H. T. Ringold. Studies in nitro steroids. Part I. The synthesis of 6α- and 6β-nitrotestosterone and 6α- and 6β- nitroprogesterone. Journal of the American Chemical Society 81:3702-3706. 1959.

4. Brown, Herbert C. and Richard F. McFarlin. Lithium tri-t-butoxyaluminohydride—A new reagent for converting acid chlorides to aldehydes. Journal of the American Chemical Society 78:252. 1956.

5. Cookson, R. C., P. G. Hamon and J. Hudee. The acid-catalyzed isomerization of cyclopropanes. Journal of the Chemical Society, 1963, p. 5782-5787.

6. Doering, W. von E., R. G. Buttery, R. G. Laughlin and N. Chaudhuri. Indiscriminate reaction of methylene with the carbon-hydrogen bond. Journal of the American Chemical Society 78:3224. 1956.

7. Doering, W. von E. and A. Kentaro Hoffmann. The addition of dichlorocarbene to olefins. Journal of the American Chemical Society 76:6162-6165. 1954.

8. Doering, W. von E. and P. LaFlamme. The cis addition of dibromocarbene and methylene to cis- and trans-butene. Journal of the American Chemical Society 78:5447-5448. 1956.

9. Fieser, Louis F. and Mary Fieser. Steroids. New York, Reinhold, 1959. 945 p.

10. Florkin, Marcel and Elmer H. Stotz. Comprehensive biochemistry. vol. 10. New York, Elsevier, 1963. 209 p.

11. Franzen, Volker. Notiz über die 1. 4-Addition von Methylen an Butadien. Chemische Berichte, 1962, p. 571-573.

12. Fried, Josef and Emily F. Sabo. 9α-fluoro derivatives of cortisone and hydrocortisone. Journal of the American Chemical Society 76:1455-1456. 1954.

13. Fried, Josef and Emily F. Sabo. Halogenated corticoids. I. 9α-halogen derivatives of cortisone and hydrocortisone. Journal of the American Chemical Society 79:1130-1141. 1957.

14. Georgian, V., J. F. Kerwin, M. E. Wolff and F. F. Owings. A new carbocyclic steroid structure: 12, 18-cyclosteroids. Journal of the American Chemical Society 84:3594-3595. 1962.

15. Geuther, A. Uber die Zersetzung des Chloroforms durch alkoholische Kalilösung. Justus Liebigs Annalen der Chemie 123:121-122. 1862.

16. Grant, F. W. and W. B. Cassie. Hexachloroacetone as a source of dichlorocarbene. Journal of Organic Chemistry 25:1433-1434. 1960.

17. Groj, O., E. P. Oliveto, C. H. Robinson and D. H. R. Barton. The preparation of 5, 9-cyclosteroids. Proceedings of the Chemical Society, 1961, p. 207-208.

18. Herz, Josef E., Josef Fried and Emily F. Sabo. 12α-halo derivatives of 11β-hydroxyprogesterone. Journal of the American Chemical Society 78:2017-2018. 1956.

19. Herzberg, G. The spectra and structures of free methyl and free methylene. Proceedings of the Royal Society (London) A262:291-317. 1961.

20. Hine, Jack. Carbon dichloride as an intermediate in the basic hydrolysis of chloroform. A mechanism for substitution reactions at a saturated carbon atom. Journal of the American Chemical Society 72:2438-2445. 1950.

21. Kadaba, Pankaja K. and John O. Edwards. Hexachloroacetone as a novel source of dichlorocarbene. Journal of Organic Chemistry 25:1431-1433. 1960.

22. Knox, Lawrence H. et al. Steroidal dihalocyclopropanes. Journal of the American Chemical Society 85:1851-1858. 1963.

23. Ledewith, A. and R. M. Bell. Reactions of dihalocarbenes with isoprene. Chemistry and Industry, 1959, p. 459-460.

24. Miller, William T., Jr. and Chung Sul Youn Kim. Reactions of alkyllithiums with polyhalides. Journal of the American Chemical Society 81:5008-5009. 1959.

25. Miller, William T., Jr. and David M. Whalen. Trichloromethyllithium, an electrophilic reagent. Journal of the American Chemical Society 86:2089-2090. 1964.

26. Müller, Von Eugen, et al. Ring-A-Homologe Steroidhormones. Justus Liebigs Annalen der Chemie 662:38-47. 1963.

27. Orchin, Milton and E. C. Herrick. Reactions of dichlorocarbene with conjugated dienes. Journal of Organic Chemistry 24:139-140. 1959.

28. Parham, William E. and Edward E. Schweizer. An improved synthesis of dichlorocarbene from ethyl trichloroacetate. Journal of Organic Chemistry 24:1733-1735. 1959.

29. Pearson, T. G., R. H. Purcell and G. S. Saigh. Methylene. Journal of the Chemical Society, 1938, p. 409.

30. Reutov, O. A. and A. N. Lovtsova. A new method for the synthesis of trichloromethyl organomercury compounds. Proceedings of the Academy of Sciences of the S.S.S.R., Chemistry Section 139:729-732. 1961. (Translated from Dokalady Akademiia Nauk)

31. Sanderson, William A. and Harry S. Mosher. Stereospecific rearrangement of neopentyl alcohol-1-**d**. Journal of the American Chemical Society 83:5033-5034. 1961.

32. Sandoval, A., G. Rosenkranz and Carl Djerassi. A steroidal cyclopropyl ketone. Journal of the American Chemical Society 73:2383-2385. 1951.

33. Seyferth, Dietmar, James M. Burlitch and James K. Heeren. A new preparation of dihalocarbenes by an organometallic route. Journal of Organic Chemistry 27:1491-1492. 1962.

34. Seyferth, Dietmar and James M. Burlitch. Concerning the mechanism of the reaction of phenyl (trihalomethyl) mercurials with olefins. Journal of the American Chemical Society 86:2730-2731. 1964.

35. Seyferth, Dietmar, et al. The reactions of phenyl (trihalomethyl) mercurials with olefins of low reactivity toward dihalocarbenes. Journal of Organic Chemistry 28:1163-1164. 1963.

36. Simmons, Howard E., Elwood P. Blanchard and Ronald D. Smith. Cyclopropane synthesis from methylene iodide, zinc-copper couple, and olefins. III. The methylene transfer reaction. Journal of the American Chemical Society 86:1347-1356. 1964.

37. Skell, P. S. and I. Starer. Reaction of alkoxide with CX_2 to produce carbonium ion intermediates. Journal of the American Chemical Society 81:4117-4118. 1959.

38. Wagner, W. M., H. Kloosterziel and S. Van Der Ven. The thermal decarboxylation of alkali trichloroacetates in aprotic solvents. Recueil des Travaux Chimiques des Pays-Bas 80:740-746. 1961.

39. Woodworth, Robert C. and Philip S. Skell. Methylene, CH_2. Stereospecific reaction with cis- and trans-2-butene. Journal of the American Chemical Society 81:3383-3386. 1959.