A Convenient Synthesis of Ketones from Certain Substituted Ethylenes. Procedure and Mechanism[1]

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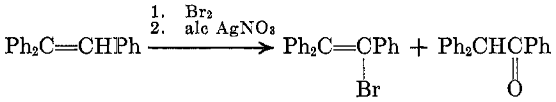
A novel method for the direct conversion of some substituted ethylenes to ketones is described. The ketone synthesis is shown to proceed with a concurrent rearrangement of the carbon skeleton. A mechanism, supported by isotopic labeling experiments, is postulated to account for the transformation.

The addition of bromine to olefins is a well-known reaction frequently used as a qualitative test for unsaturation. The products of such additions are usually the corresponding dibromides. However, in at least two reported[4,5] instances ketones have been isolated as by-products.

In the first of these reports,[4] the bromination of triphenylethylene (1) in either chloroform or glacial acetic acid, followed by decomposition with alcoholic silver nitrate, has been reported to give triphenylethylene bromide (2) as well as variable quantities of phenyl benzhydryl ketone (3).

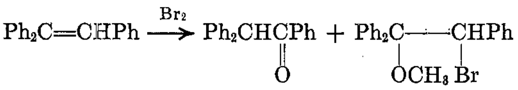


$$\mathrm{Ph_2C{=}CHPh} \xrightarrow{\substack{\text{1. Br}_2\\ \text{2. alc AgNO}_3}} \mathrm{Ph_2C{=}\underset{\underset{\textstyle Br}{|}}{C}Ph} + \mathrm{Ph_2CH\underset{\underset{\textstyle O}{\|}}{C}Ph}$$

1 2 3

The same report described some of the experimental conditions which affect the nature and composition of the products.

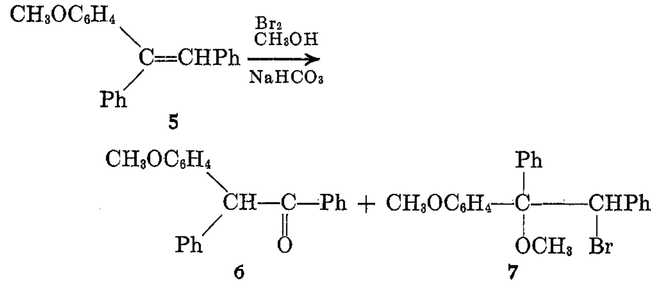
A similar bromination of triphenylethylene, this time in methanol, was found[5] to give a mixture of phenyl benzhydryl ketone (3) and 2-bromo-1-methoxy-1,1,2-triphenylethane (4).



$$\mathrm{Ph_2C{=}CHPh} \xrightarrow{\text{Br}_2} \mathrm{Ph_2CH\underset{\underset{\textstyle O}{\|}}{C}Ph} + \mathrm{Ph_2\underset{\underset{\textstyle OCH_3}{|}}{C}{-}\underset{\underset{\textstyle Br}{|}}{C}HPh}$$

1 3 4

This report also describes the conversion of *cis*- and *trans*-1-(*p*-anisyl)-1,2-diphenylethylene (5) to 1-keto-2-(*p*-anisyl)-1,2-diphenylethane (6) and 1-(*p*-anisyl)-2-bromo-1-methoxy-1,2-diphenylethane (7). The bromo compounds 4 and 7 were found[5] to rearrange to ketones 3 and 6 when treated with alcoholic silver nitrate.



5

6 7

Despite these reports, to our best knowledge, a systematic study of the mechanism which can account for the ketone formation has never been undertaken. Furthermore, the potential synthetic utility of these reactions has not been fully explored. Consequently, we felt that it would be of considerable theoretical as well as practical interest to investigate the mechanism of these transformations and to establish a generally useful synthetic procedure for the direct conversion of certain substituted ethylenes to the corresponding ketones.

Our investigation consisted of three phases. First we directed our efforts toward the determination of the optimum experimental conditions for obtaining the maximum yield of ketones from the corresponding substituted ethylenes. We then tried to get some insight into the mechanism of the rearrangement by means of isotopic labeling and other techniques. Finally we sought to determine the scope of the procedure by preparing a number of substituted ethylenes and subjecting them to the same experimental conditions which were identified in the first part of our study as producing maximum yield of ketones.

For convenience each of these phases of our work will be discussed individually.

Results and Discussion

Maximizing the Yield of the Rearranged Products.—Since the rearrangement was first observed with triphenylethylene, most of our initial trials were conducted with this compound. The object was to discover the experimental conditions which would augment the yield of ketone, thus making it the main product instead of a by-product.

In this connection we conducted numerous experiments involving repetitive bromination reactions of triphenylethylene and other olefins, each time varying one of the experimental parameters and observing the effect that this variation had on the yield of the corresponding ketones.

The variables consisted of (1) the reaction temperature, (2) the reaction time, (3) the type of solvent used, (4) the nature of the decomposition reagent, (5) the solvent used in preparing the decomposing solution, (6) the contact time with the decomposition reagent, (7) the size of the run, and (8) the molar ratio of bromine to olefin. After each experiment the reaction mixtures were examined by thin layer chromatography and nmr and infrared spectroscopy. The components of the mixtures were whenever possible separated by column chromatography and identified.

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(1) (a) This paper was presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969; (b) support of this work by grants from the Research Corporation is gratefully acknowledged.

(2) To whom inquiries should be directed.

(3) Master of Arts in Teaching Chemistry Thesis, Chapman College, Nov 1968.

(4) S. Apelgot, A. Cheutin, S. Mars, and M. R. Berger, *Bull. Soc. Chim. Fr.*, **19**, 533 (1952).

(5) D. Y. Curtin and E. K. Meislich, *J. Amer. Chem. Soc.*, **74**, 5518 (1952).

Since this phase of our investigation involved several hundred trials it is both impossible and unnecessary to describe each experiment in detail. Instead we will enumerate and discuss only the most important of our findings which can be summarized as follows.

1. The formation of the ketones occurs in the workup, since the infrared spectra of the brominated reaction mixtures show no carbonyl absorption band before decomposition and strong carbonyl absorption band right after decomposition. This explains why the ketone formation could not be prevented by excluding oxygen from the reaction as was attempted by Apelgot, *et al.*,[4] who erroneously sought an explanation for the ketone formation in the bromination reaction itself.

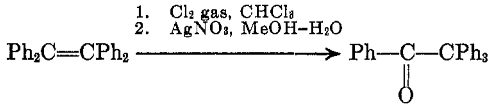
2. The elimination of hydrogen bromide gas in many instances competes with the ketone formation and gives rise to vinyl bromides which are unreactive toward silver nitrate or any of the other decomposition reagents tried. This observation provides the clue for the profound effect that the reaction temperature and time have on the nature and composition of the products. In general, lower temperatures and short reaction times favor the formation of ketones, whereas at high temperatures or long reaction times the principal products are vinyl bromides. This is because at low temperatures the initially formed dibromides are more stable; thus hydrogen bromide gas elimination is considerably slower and the bulk of the substrate remains in a form which is reactive toward silver nitrate. Similarly, the longer the reaction time the greater the proportion of the substrate which has been transformed into the unreactive vinyl bromide. This explanation is supported by the fact that the reactions of tetrasubstituted ethylenes, where hydrogen bromide gas elimination is not possible, are not affected by variations in the reaction temperature and time. Consequently such compounds are readily converted to ketones by our procedure, subject only to the limitations described in the last part of the discussion section.

3. The presence of water is essential to the formation of the ketone. During several trials in which anhydrous alcoholic silver nitrate was used no ketones were formed. However, duplicate runs, under identical conditions except for the use of alcoholic silver nitrate containing at least 5% water, readily generated ketones. The role of water was further investigated by oxygen-18 labeling and will be discussed in detail in the next part of this section.

4. Several other reagents, such as solutions of mercuric and lead salts, activated alumina, silver hydroxide, or simply alcohol–water mixtures, were also found to promote the ketone formation; however, the conversion is much slower, the product mixtures are more complex, and the yields of ketone are generally much lower than those obtained when alcoholic silver nitrate is used.

In a few instances, silver carbonate precipitated on Celite, a mixture known as "Fetizon's Reagent,"[6] was found to be superior to alcoholic silver nitrate in bringing about the rearrangement to the ketone. A more detailed discussion of the reactions involving this reagent will be presented in the last part of this section.

5. The action of alcoholic silver nitrate on chlorinated substrates can also promote conversion to ketones. Although it is generally more convenient to work with bromine, with some compounds chlorine must be used. In the case of tetraphenylethylene (**8**) for example, which is unreactive toward bromine, we tried our procedure with chlorine, passing the gas through a chloroform solution of the olefin. Upon decomposition with alcoholic silver nitrate a nearly quantitative yield of phenyltrityl ketone (**9**) was obtained. This conversion is incidentally an example of the favorable special cases of tetrasubstituted ethylenes, previously discussed, where the competitive elimination of hydrogen halide gas cannot take place.



$$\mathrm{Ph_2C{=}CPh_2} \xrightarrow{\substack{\text{1. Cl}_2\text{ gas, CHCl}_3 \\ \text{2. AgNO}_3\text{, MeOH-H}_2\text{O}}} \mathrm{Ph{-}\underset{\underset{O}{\|}}{C}{-}CPh_3}$$

8 **9**

6. The necessary contact time with the alcoholic silver nitrate for ketone formation is proportional to the stability of the dihalide substrate. With very labile dihalides the rearrangement takes places within minutes. With relatively stable dihalides several hours of stirring with the decomposition solution may be necessary for complete precipitation of the silver halide salts. In most cases overnight contact is sufficient.

7. The choice of solvent for carrying out the bromination reaction and for making up the bromine solutions has an important bearing on the outcome of the reaction. Nucleophilic solvents are generally unsatisfactory and give rise to complex mixtures of products where one or both of the halogen atoms have been substituted by nucleophilic species from the solvent. This results in lowering the yields of ketones and making their isolation and characterization difficult. The solvent also must be such that the substrates retain high solubility in it, even at very low temperatures. Thus from the various solvents tested (ether, dioxane, hexane, carbon tetrachloride, various alcohols, glacial acetic acid, etc.) we have found chloroform to be generally the most suitable.

8. The molar ratio of bromine to olefins has no effect on the nature and composition of the products; however, a large excess of bromine necessitates inordinate amounts of silver nitrate solution and thus should be avoided.

9. The per cent yield of ketone is independent of the size of the run. Thus our procedure can be equally applied to large as to small scale preparations of ketones.

Summarizing the above findings the best conditions for ketone formation are as follows: Dry Ice temperature, the shortest possible reaction time, chloroform solvent for both the olefin and the bromine, decomposition of the brominated mixtures with methanolic silver nitrate containing 5–12% water (higher water content gives rise to unsatisfactory two-phase systems), and the allowance of sufficient time for complete precipitation of the silver halide salts.

When the above procedure is followed, high and often quantitative yields of ketones are obtained from the corresponding olefins, subject only to the limitations discussed in the last part of this section.

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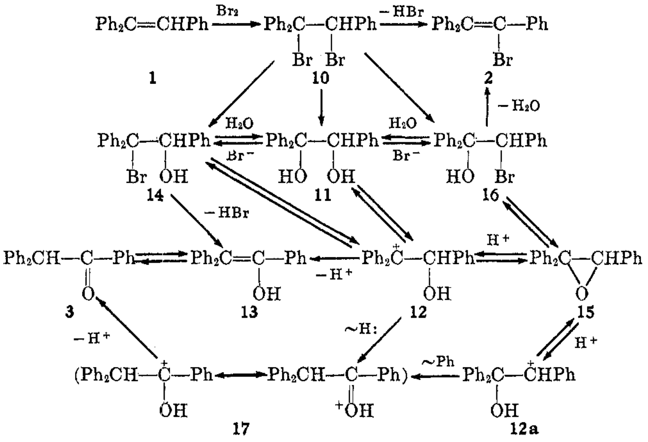
[6] M. Fétizon and M. Golfier, *C. R. Acad. Sci., Ser. C*, **276**, 900 (1968).

Mechanistic Studies.—As before, the principal model for these studies was triphenylethylene. Some of the clues as to the mechanism of the ketone formation were provided by the experiments described in the previous part of this section. However, there still remained several theoretically plausible pathways by means of which the conversion could have taken place. Consequently we have proceeded to list the various mechanistic alternatives and to perform experiments which would allow us to differentiate among them.

The possibilities which have been ruled out by our experiments are summarized in Scheme I. One possible sequence could involve the formation of the dibromide **10** from triphenylethylene (**1**) followed by direct or indirect hydrolysis of this compound to the glycol **11**, an identified[7] precursor of phenyl benzhydryl ketone (**3**) *via* the well-known pinacol rearrangement.[8]

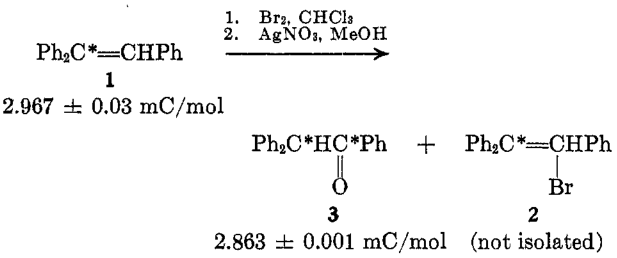
SCHEME I

THEORETICALLY PLAUSIBLE MECHANISTIC PATHS FOR THE CONVERSION OF TRIPHENYLETHYLENE TO PHENYL BENZHYDRYL KETONE

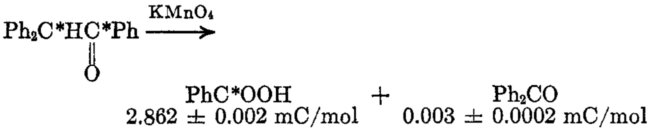


This rearrangement can theoretically[9] take place in two ways: either through the carbonium ion **12** followed by a hydride shift or through the enol form **13**. The latter can also derive from the bromohydrin **14** by elimination of hydrogen bromide gas. The same bromohydrin **14** can also, theoretically, give rise to the carbonium ion **12** following the removal of the bromide by silver nitrate. The role of the carbonium ion **12a** can be safely neglected since its contribution to the pinacol rearrangement of **11** has been shown[7] to be insignificant.

To test for these possibilities we have subjected a sample of 1,1,2-triphenylethylene-*1*-^{14}C (**1**) to our bromination and silver nitrate decomposition procedure as outlined in the Experimental Section. After two crystallizations from methanol, an 88% yield of pure (mp 139–140°) phenyl benzhydryl ketone-^{14}C (**3**) was obtained. The ketone was subsequently oxidized to benzophenone and benzoic acid by the method of Bonner and Collins;[10] the fragments were assayed for radioactivity. These transformations can be illustrated by the following equations. (The double asterisk designates uncertainty as to the position of the label and not double labeling.)



$$\underset{\substack{\mathbf{1}\\ 2.967 \pm 0.03\ \mathrm{mC/mol}}}{\mathrm{Ph_2C^*{=}CHPh}} \xrightarrow[\text{2. AgNO}_3\text{, MeOH}]{\text{1. Br}_2\text{, CHCl}_3} \underset{\substack{\mathbf{3}\\ 2.863 \pm 0.001\ \mathrm{mC/mol}}}{\mathrm{Ph_2C^*H\underset{\underset{O}{\|}}{C}{}^*Ph}} + \underset{\substack{\mathbf{2}\\ \text{(not isolated)}}}{\mathrm{Ph_2C^*{=}\underset{\underset{Br}{|}}{C}HPh}}$$



$$\mathrm{Ph_2C^*H\underset{\underset{O}{\|}}{C}{}^*Ph} \xrightarrow{\mathrm{KMnO_4}} \underset{2.862 \pm 0.002\ \mathrm{mC/mol}}{\mathrm{PhC^*OOH}} + \underset{0.003 \pm 0.0002\ \mathrm{mC/mol}}{\mathrm{Ph_2CO}}$$

Our radiochemical data, given above, showed that all of the label resided in the benzoic acid fraction. Thus the conversion of triphenylethylene to phenyl benzhydryl ketone by our method was found to proceed with 100% phenyl migration. This rules out the participation of either the carbonium ion **12** or the bromohydrin **14** as intermediates in the present rearrangement, since in each of those instances the carbon skeleton would have remained unrearranged. The same data also rule out the intervention of the enol form **13**. Nevertheless, since the enol form was shown as the ketone precursor when our procedure was cited by Fieser,[11] we have conducted an additional experiment for further confirmation. The bromination of triphenylethylene was carried out as usual except that this time the mixture was decomposed with methanolic silver nitrate prepared with 90% deuteriomethanol (CH_3OD) and 10% D_2O.

The reaction afforded a 90% yield of pure (mp 139–140°) phenyl benzhydryl ketone. The integrated nmr spectrum of the product showed no incorporation of deuterium. Furthermore, when an authentic sample of the deuterated ketone $Ph_2CDCOPh$ (99.5% deuterium) was subjected to our experimental conditions and examined by nmr all of the original label had been retained. Since the enol form **13** of phenyl benzhydryl ketone undergoes deuterium exchange readily, we have concluded that it cannot be a precursor of phenyl benzhydryl ketone in the present case.

It has been known for some time[12] that triphenylethylene oxide (**15**) can under certain conditions revert to phenyl benzhydryl ketone. However, its involvement in the present rearrangement is highly unlikely for two reasons. First, under the fairly mild acidic conditions of our experiment this compound has been found[13] to give not phenyl benzhydryl ketone (**3**) but the glycol **11**. Second, for the ketone production to proceed *via* the epoxide in a manner consistent with our radiochemical findings, the ring opening must take place in such a way as to produce the carbonium ion **12a** exclusively. This is entirely unreasonable since the alternate carbonium ion **12** is the more stable of the two. Hence if the epoxide **15** was a precursor of the ketone one would have expected the integrity of the carbon skeleton to be preserved at least in part.

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(7) C. J. Collins, *J. Amer. Chem. Soc.*, **77**, 5517 (1955). This paper contains all the pertinent earlier references.

(8) C. J. Collins, *Quart Rev. Chem. Soc.*, **14**, 357 (1960).

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1962, p 602.

(10) W. A. Bonner and C. J. Collins, *J. Amer. Chem. Soc.*, **75**, 5378 (1953).

(11) M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, pp 367, 368.

(12) R. Lagrave, *Ann. Chim.*, **8**, 363 (1927).

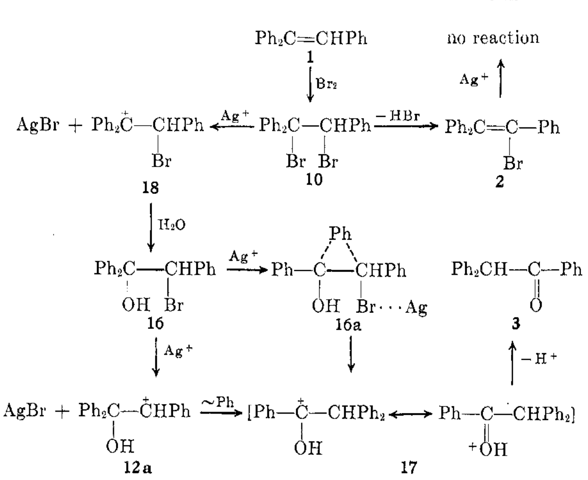
(13) J. F. Lane and D. R. Walters, *J. Amer. Chem. Soc.*, **73**, 4234 (1951).

Since our labeling experiments showed conclusively that a 100% rearrangement has taken place, we are forced to rule out this possibility.

In view of the above, only one reasonable mechanism remained which was consistent with our data; it is summarized in Scheme II. The proposed mechanism postulates the initial formation of the dibromide **10**, which then can either remain intact to undergo further transformations during the work-up or eliminate hydrogen bromide gas, irreversibly producing the vinyl bromide **2**, which is unreactive toward silver nitrate. The profound effect of the reaction temperature and time on this competition between the elimination of hydrogen bromide gas and the formation of the ketone has already been discussed and explained in the previous part of this section. This explanation is supported by the findings of Meisenheimer,[14] who has prepared the dibromide **10** and reported that it does in fact decompose on standing or heating to the vinyl bromide **2**. It is therefore the portion of the dibromide **10** which remains unchanged that undergoes nucleophilic substitution either with water or other nucleophiles, *e.g.*, methanol. The latter possibility will account for the reported[5] isolation of such products as 2-bromo-1-methoxy-1,1,2-triphenylethane described in the beginning of this paper.

SCHEME II

POSTULATED MECHANISM FOR THE CONVERSION OF TRIPHENYLETHYLENE TO PHENYL BENZHYDRYL KETONE



In the absence of silver nitrate these substitutions as well as the subsequent reactions of that system are slow and cannot effectively compete with the hydrogen bromide gas elimination. Thus only minor yields of ketones are obtained from the process. On the other hand the interaction of the dibromide **10** with silver nitrate accelerates the reaction by facilitating removal of the bromide from the carbon bearing the two phenyl groups. This is most likely an S_N1 process involving the initial formation of the rather stable carbonium ion **18**; however, our data do not permit differentiation between this and the alternate S_N2 process. When water is the nucleophile the product of the above substitution is the bromohydrin **16**. The involvement of water as the oxygen source for the ketone formation was suggested by the fact that anhydrous decomposition reagents failed to produce the ketone. To obtain further confirmation we have conducted the bromination of triphenylethylene under the usual conditions except that the decomposition reagent consisted of a saturated silver nitrate solution made up with anhydrous methanol (95%) and oxygen-18 enriched water (5%). The isotopic enrichment of the water was 3 atom per cent. The phenyl benzhydryl ketone thus produced was examined by mass spectrometry.

The mass spectrum contained no molecular ion. However it showed two fragmentation peaks at masses 107 and 105 corresponding to the fragments $PhCH^{18}O$ and $PhCH^{16}O$, respectively. The ratio of these peaks was 1.5:1. To preclude the possibility of exchange after the ketone was formed, an authentic sample was subjected to the same reaction conditions and the mass spectrum of the recovered material was examined. This spectrum showed a peak ratio of mass 107 to mass 105 of 0.5:1, most likely due to the double carbon-13 isotope.

The data thus indicated a net incorporation of oxygen-18 from the water to the ketone of 1%.

Since the isotopic enrichment of the water was 3 atom %, two-thirds of the label remained unaccounted for. We can offer only one explanation for this discrepancy: it may be due to a combination of a kinetic isotope effect and preliminary oxygen exchange between the water and the nitrate ions of the decomposing solution. Such exchanges under acidic conditions are sometimes known[15] to occur.

Continuing with our postulated mechanism we propose further that the initially formed bromohydrin **16** undergoes semipinacolic dehydrobromination catalyzed by silver ions and accompanied by phenyl migration. This may theoretically be a one-step process *via* the transition state **16a** or a two-step process involving the formation of carbonium ion **12a** followed by phenyl migration. Our data do not permit differentiation between these two possibilities. However, for reasons already stated the intervention of **12a** is highly unlikely. In either case the product is the protonated ketone **17** which reverts to phenyl benzhydryl ketone (**3**) by a proton transfer.

This type of rearrangement of halohydrins to ketones is well known.[13,16] Furthermore, the transformation of the bromohydrin **16** to phenyl benzhydryl ketone under a variety of conditions has already been reported by Lane and Walters.[13] Finally, Bonner and Collins[17] have radiochemically demonstrated that the ketone formation takes place with complete phenyl migration. As a further confirmation an authentic sample of the bromohydrin **16** was synthesized and subjected to our experimental conditions, following a procedure identical with the bromination and decomposition of the triphenylethylene samples. A quantitative yield of phenyl benzhydryl ketone was obtained from the above reaction.

It is evident from the preceding discussion that the mechanism we have postulated is not only consistent with our own data but also strongly supported by the

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(14) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **456**, 126 (1927).

(15) R. Klein and R. A. Friedel, *J. Amer. Chem. Soc.*, **72**, 3810 (1950).

(16) (a) D. Y. Curtin and E. K. Meilich, *ibid.*, **74**, 5905 (1952). (b) For a complete discussion see G. W. Wheland, "Advanced Organic Chemistry," Wiley, New York, N. Y., 1960, Chapter 12.

(17) W. A. Bonner and C. J. Collins, *J. Amer. Chem. Soc.*, **75**, 5379 (1953).

findings of other investigators. We therefore believe it to be the correct mechanism for the transformation of substituted ethylenes to ketones by our previously described procedure.

Establishing the Scope of the Procedure.—In the last part of our work, we sought to test the generality of our method of olefin conversion to ketones and to examine its relative merits from the point of view of synthesis. To this end a number of substituted ethylenes were prepared by action of appropriate Grignard reagents on ketones or esters, followed by dehydration of the resulting tertiary alcohols or by the Wittig reaction.[18] The olefins obtained in this manner were then subjected to our bromination and decomposition procedure as described at the end of the first part of this section. A number of commercial products as well as samples supplied by private sources were also tested.

The results of these experiments are summarized in Table I, which shows the principal carbonyl compounds obtained in each case and the approximate yields. The list was meant to be representative of the various types of substituted ethylenes rather than exhaustive. The data obtained from the reactions of these compounds permit us to make certain generalizations regarding the usefulness of our procedure for converting substituted ethylenes to carbonyl compounds.

We can generally conclude that our method will work best with highly substituted ethylenes providing that at least some of the substituents are aromatic. The presence of such substituents on the ethylenic carbons stabilizes the incipient carbonium ions, thus resulting in the formation of dihalides which are quite reactive toward silver nitrate. Thus the yields of ketones decrease as the proportion of alkyl substituents increases and the procedure fails completely with systems that have only aliphatic substituents. With such compounds a modified procedure employing somewhat more drastic conditions was tried. It consisted of brominating the olefins at room temperature in either chloroform or carbon tetrachloride followed by decomposition with silver carbonate–Celite reagent.[6]

After stirring for several hours either at room temperature or under reflux, low yields of ketones were obtained. The product mixtures were, however, complex, containing the brominated compounds, some starting material, and variable quantities of substitution products such as cyclic carbonates. We are now in the process of evaluating further the potential uses of the silver carbonate–Celite reagent, attempting to discover conditions which will minimize the yields of undesirable products.

With either procedure, if the substituents on the ethylenic carbon atoms are not all the same, mixtures of ketonic products may of course result. The composition of these mixtures will then depend on the relative migration tendencies of the substituents and the stereochemical requirements of the molecules. The separation of the various components in these mixtures proved to be difficult and hence was not pursued. Consequently, in all such cases, only the principal component was identified and listed in Table I. The stated yield, however, is the total yield of the ketonic products.

It is noteworthy, from the point of view of synthesis, that often when low yields of ketones were obtained, a substantial portion of the reaction mixture was unchanged starting material. Thus, at least in some instances, it is possible to augment the yield of ketones by recycling. Other important features of our process are the extremely mild conditions and the very short reaction time. These make it possible to achieve conversion of certain olefins to ketones even when other sensitive groups are present in the same molecule.

Taking into account the various limitations which we have outlined above, it can be concluded that our process can be conveniently applied to a large number of substituted ethylenes, converting them directly to ketones in high yields.

Although our initial studies were confined to simple compounds, further studies are now in progress, exploring the reactions of more complex systems such as mono- and polycyclic olefins. We are also investigating the potential application of this rearrangement to the synthesis and degradation of natural products.

Experimental Section[19]

I. Isotopically Labeled Compounds[20] and Experiments. Radioactivity Assays.—Radioactivity levels of the various carbon-14 labeled compounds were determined by dry combustion of the samples to carbon dioxide which was collected in an ionization chamber and assayed in the usual way,[21] using a Cary Model 31 vibrating-reed electrometer.

All determinations were performed in triplicate, the reported values being the average of these determinations.

1,1,2-Triphenylethylene-*1*-^{14}C (1).—This compound was prepared by the reaction of benzylmagnesium chloride with carbonyl-labeled benzophenone,[22] followed by the formic acid dehydration of the resulting 1,1,2-triphenylethanol-*1*-^{14}C. The procedure used was essentially that of Adkins and Zartman.[23] After chromatography on an alumina column and several recrystallizations from ethanol an analytically pure (mp 71–72°) sample of 1,2,2-triphenylethylene-*1*-^{14}C (specific activity 2.967 ± 0.03 mCi/mol) was obtained. The identity of the sample was established by comparing its infrared spectrum with that of an authentic sample.

Phenyl Benzhydryl Ketone-^{14}C (3).—A sample of 1,1,2-triphenylethylene-*1*-^{14}C (2 g, *ca.* 0.00782 mol, specific activity 2.967 ± 0.03 mCi/mol, mp 71–72°) was converted to phenyl benzhydryl ketone-^{14}C by the application of method B as outlined in the next part of this section. The crude product (1.92 g, 90%, mp 136–138°) was purified by successive crystallizations from ethanol. Thus 1.87 g (88%) of pure (mp 139–140°) phenyl benzhydryl ketone-^{14}C (specific activity 2.863 ± 0.001 mCi/mol) was obtained. The infrared spectrum of this product matched that of an authentic sample.

Oxidative Degradation of Phenyl Benzhydryl Ketone-^{14}C.—A sample of the above phenyl benzhydryl ketone-^{14}C (1.77 g, 0.00614 mol, specific activity 2.863 ± 0.001 mCi/mol) was oxidized to benzoic acid and benzophenone using potassium permanganate dissolved in aqueous acetone, adapting the procedure of Bonner and Collines.[10] Yields of the oxidation products were

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(18) A. Maercker, *Org. React.*, **14**, 270 (1965).

(19) Melting points were taken on a Thomas-Hoover "Uni-Melt" apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A or T-60 spectrometer, with tetramethylsilane as an internal standard. Infrared spectral data were recorded on Beckman IR-8 or Perkin-Elmer 457 spectrometers. Vpc analysis of liquid samples was performed with a Varian Aerograph 90-P chromatograph. Mass spectra were obtained with a consolidated CEC 110 high resolution mass spectrometer at Union Oil Research Center, Brea, Calif.

(20) All isotopically labeled compounds were synthesized by Dr. Frederic J. Kakis at Oak Ridge National Laboratory, Oak Ridge, Tenn., under a Research Participation Fellowship. Radioactivity determinations were also performed during that period.

(21) V. A. Raaen and G. A. Ropp, *Justus Liebigs Ann. Chem.*, **25**, 174 (1953).

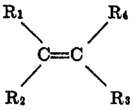
(22) From Oak Ridge National Laboratory.

(23) H. Adkins and W. Zartman, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 606.

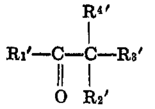
TABLE I

SUBSTITUTED ETHYLENES TESTED AND THEIR MAIN REARRANGEMENT PRODUCTS

Alkene

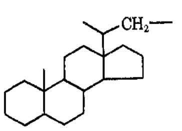


Principal carbonyl product

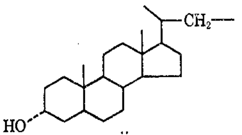


No	R$_1$	R$_2$	R$_3$	R$_4$	R$_1$'	R$_2$'	R$_3$'	R$_4$'	Yield, %[a]	Method[b]
1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	94	A
2	Ph	Ph	Me	Ph	Ph	Me	Ph	Ph	88	A
3	Ph	Ph	Me	H	Ph	Me	Ph	H	85	B
4	Ph	Ph	*n*-Octyl	H	Ph	Ph	*n*-Octyl	H	87	B
5	Ph	Ph	Ph	H	Ph	Ph	Ph	H	96	B
6	*p*-MePh	*p*-MePh	*p*-MePh	H	*p*-MePh	*p*-MePh	*p*-MePh	H	95	B
7	*p*-CH$_3$OPh	*p*-CH$_3$OPh	*p*-CH$_3$OPh	H	*p*-CH$_3$OPh	*p*-CH$_3$OPh	*p*-CH$_3$OPh	H	94	B
8[c]	Ph	*p*-CH$_3$OPh	*o*-MePh	H	Ph	*p*-CH$_3$OPh	*o*-MePh	H	85	B
9[c]	Ph	3,4-Me$_2$Ph	3,4-Me$_2$Ph	H	3,4-Me$_2$Ph	3,4-Me$_2$Ph	Ph	H	82	B
10[c]	Ph	1-Naphtyl	Ph	H	1-Naphtyl	Ph	Ph	H	60	B
11[c]	Ph	2,4-Me$_2$Ph	2,4-Me$_2$Ph	H	2,4-Me$_2$Ph	Ph	2,4-Me$_2$Ph	H	78	B
12[c]	Ph	2,5-Me$_2$Ph	*p*-MePh	H	2,5-Me$_2$Ph	Ph	*p*-MePh	H	72	B
13[c]	Ph	2,5-Me$_2$Ph	*o*-MePh	H	2,5-Me$_2$Ph	Ph	*o*-MePh	H	70	B
14[c]	Ph	2,4-Me$_2$Ph	*o*-MePh	H	2,4-Me$_2$Ph	Ph	*o*-MePh	H	68	B
15[c]	Ph	H	*p*-CH$_3$OPh	*p*-MePh	*p*-MePh	Ph	*p*-CH$_3$OPh	H	86	B
16[c]	Ph	2,5-Me$_2$Ph	Ph	H	2,5-Me$_2$Ph	Ph	Ph	H	85	B
17[c]	Ph	3,4-Me$_2$Ph	Ph	H	3,4-Me$_2$Ph	Ph	Ph	H	82	B
18[c]	Ph	2,4-Me$_2$Ph	Ph	H	2,4-Me$_2$Ph	Ph	Ph	H	78	B
19[c]	Ph	*p*-MePh	Ph	H	Ph	Ph	*p*-MePh	H	86	B
20[c]	Ph	*m*-MePh	Ph	H	Ph	Ph	*m*-MePh	H	76	B
21	*p*-MePh	*p*-MePh	Ph	H	*p*-MePh	*p*-MePh	Ph	H	95	B
22[c]	Ph	*o*-MePh	Ph	H	*o*-MePh	Ph	Ph	H	76	B
23[c]	Ph(CH$_2$)$_3$–	Ph	Ph	H	H	Ph	Ph	Ph(CH$_2$)$_3$–	62	B
24[c]	Ph	*p*-ClPh	Ph	H	*p*-ClPh	Ph	Ph	H	45	B
25[c]	Ph	*p*-ClPh	3,4-Me$_2$Ph	H	*p*-ClPh	Ph	3,4-Me$_2$Ph	H	42	B
26[c]	*p*-Biphenyl	Ph	Ph	H	Ph	Ph	*p*-Biphenyl	H	84	B
27[c]	*p*-CH$_3$OPh	*p*-CH$_3$OPh	Steroid[e]	H	*p*-CH$_3$OPh	*p*-CH$_3$OPh	Steroid[e]	H	78	B
28	*p*-CH$_3$OPh	*p*-CH$_3$OPh	Steroid[f]	H	*p*-CH$_3$OPh	*p*-CH$_3$OPh	Steroid[f]	H	72	B
29[d]	*p*-CH$_3$OPh	*p*-CH$_3$OPh	H	H	*p*-CH$_3$OPh	*p*-CH$_3$OPh	H	H	62	B + C
30[d]	Ph	H	Me	H	H	Ph	Me	H	82	C
31[d]	Me	Me	Me	Me	Me	Me	Me	Me	58	C'
32[d]	Me	Me	Me	H	Me	Me	Me	H	38	C'
33[d]	Ph	Me	H	H	Ph	Me	H	H	55	C'
34[d]	Ph	Me	H	H	Me	Ph	H	H	60	B + C
35[d]	Me	Me	Et	H	Me	Me	Et	H	15	C'
36[d]	Me	H	Et	H	Et	Me	Me	H	10	C'
37[d]	1-Methylcyclohexene				1-Methylcyclohexanone					

[a] Often estimated from spectral and chromatographic data. In the event of mixtures the stated yield is the total yield of carbonyl compounds in the mixture. [b] See Experimental Section. [c] A mixture of threo and erythro or cis and trans isomers. [d] Procedure B failed with these compounds. [e] See structure i. [f] See structure ii.



i



ii

quantitative. The benzoic acid was purified by recrystallization from water followed by sublimation, mp 122.4–123.2°.

The benzophenone product was converted in the usual way into its 2,4-dinitrophenylhydrazone, which was purified by successive recrystallizations from ethyl acetate, mp 240.6–241.6°.

Radioactivity assays of these products showed that the benzoic acid fraction had retained all of the label (specific activity 2.862 ± 0.002 mCi/mol), whereas the benzophenone fraction was for all practical purposes nonradioactive (specific activity 0.003 ± 0.0002 mCi/mol).

Thus it was radiochemically demonstrated that the conversion of 1,1,2-triphenylethylene-*1*-^{14}C to phenyl benzhydryl ketone-^{14}C by method B was accompanied by 100% phenyl migration.

Chain Deuterium Labeled Phenyl Benzhydryl Ketone.—A sample of pure (mp 139–140°) phenyl benzhydryl ketone was dissolved in reagent grade toluene and treated under reflux with successive portions of pure (99.8%) D$_2$O made basic by the addition of lithium metal. A specially constructed pressure addition funnel, equipped with a two-way stopcock and an outlet, permitted the withdrawal of the exchanged portions of D$_2$O.

The incorporation of deuterium in the sample was followed by nmr by observing the gradual disappearance of the singlet proton peak at δ 6 ppm, relative to TMS (δ 0 ppm). In this fashion a sample of Ph$_2$CDCOPh (99.5%) was obtained. The deuterated sample was subjected to the reaction conditions described in the next part of this section, under method B, after which it was reisolated and its nmr spectrum reexamined. It was found that all of the original deuterium label had been retained.

Rearrangement of Triphenylethylene in a Deuterated Medium.—A sample (1.0 g, 0.0039 mol) of pure (mp 71–72°) triphenylethylene was subjected to the experimental conditions described in the next part of this section under method B, except that the decomposing reagent consisted of a saturated solution of silver nitrate made up with D$_2$O (10% by volume) and CH$_3$OD (90% by volume). The yield of crude (mp 132–134°) phenylbenzhydryl ketone was quantitative. After two recrystallizations from methanol, 0.96 g (90%) of the pure ketone (mp 139–140°) was obtained. The integrated nmr spectrum of the pure product showed that no deuterium had been incorporated into the ketone under these conditions.

Rearrangement of Triphenylethylene to Phenyl Benzhydryl Ketone in the Presence of Oxygen-18.—The object of this experiment was to determine whether oxygen-18 label from the water in the silver nitrate reagent is incorporated into the rearrangement product, phenyl benzhydryl ketone. The ketone, however, could conceivably undergo isotopic exchange after it is formed. To minimize this possibility, and in view of the fact that the yield was not important in this case, a procedure was sought which would, in the shortest possible reaction time, give a reasonable amount of relatively pure product. The conditions were worked out during several preliminary trials with unlabeled reagents.

Thus triphenylethylene (1 g, 0.0039 mol, mp 71–72°) was dissolved in spectral grade chloroform (25 ml) and cooled in a Dry Ice–isopropyl alcohol bath. The mixture was stirred magnetically and treated with a 5% solution of bromine in chloroform (4.1 ml) in a flask fitted with a drying tube.

Subsequently a saturated silver nitrate solution (35 ml), prepared with anhydrous methanol (95% by volume) and oxygen-18 enriched (3 atom %) water (5% by volume), was added to the reaction mixture and the stirring continued for 15 min. To remove the silver salts and achieve rapid drying three successive suction filtrations through layers of anhydrous magnesium and sodium sulfates were performed.

After removal of the solvents by rotatory evaporation a white solid was obtained which was purified by dissolving it in boiling ethanol, filtering the hot solution to remove insoluble impurities, and cooling at zero degrees overnight. The resulting crystals were collected by suction filtration and dried under vacuum over phosphorus pentoxide (0.31 g, 52%, mp 133–135°).

A sample of this product, identified by its infrared spectrum as phenyl benzhydryl ketone, was without further purification (for fear that it might undergo isotopic exchange) submitted for mass spectrometric analysis.

The mass spectrum showed two fragmentation peaks at masses 107 and 105 corresponding to the fragments PhCH^{18}O and PhCH^{16}O respectively. The ratio of these peaks was 1.5:1. However, when an authentic sample of phenyl benzhydryl ketone was subjected to the above reaction conditions and the mass spectrum of the recovered material was examined it showed a ratio of the same peaks of 0.5:1. Thus the net incorporation of oxygen-18 from the water to the ketone was found to be of the order of 1%.

II. Unlabeled Compounds and Experiments. Synthesis and Rearrangement of 2-Bromo-1,1,2-triphenylethanol.—An authentic sample of 2-bromo-1,1,2-triphenylethanol was prepared by the method of Lane and Walters,[13] and purified by filtration through decolorizing charcoal and recrystallization from hexane.

A sample (0.91 g) of the purified material (mp 123–124°) was then dissolved in chloroform (25 ml) and subjected to the conditions of method B described below. This resulted in the isolation of a quantitative yield (0.69 g, 98%) of crude (mp 133–135°) phenyl benzhydryl ketone. After one recrystallization from ether, 0.61 g (92%) of pure (mp 139–140°) phenyl benzhydryl ketone was obtained.

Substituted Ethylenes.—A complete list of the substituted ethylenes used in our study appears in Table I. Compounds 1 and 30–37 are commercial samples obtained from various sources and used without further purification. Compounds 2–4 and 27–28 were privately supplied.[24] All the other compounds were prepared by standard Grignard reactions of appropriate aryl- or alkylmagnesium halides with substituted benzophenones, deoxybenzoins, or esters. Some of the resulting tertiary alcohols underwent spontaneous dehydration during the work-up, generating the corresponding substituted ethylenes. The remainder were dehyrated by means of formic acid containing some *p*-toluenesulfonic acid. A few compounds were prepared by the Wittig reaction.[18]

This process in most cases gave mixtures of either cis and trans or threo and erythro isomers.

The separation of these isomers proved to be difficult and time consuming and was therefore abandoned. Instead the mixtures were directly subjected to the rearrangement methods described below.

Rearrangement of Substituted Ethylenes to Aldehydes or Ketones.—The following methods for converting substituted ethylenes to carbonyl compounds have resulted from numerous preliminary trials during which the conditions which would produce the maximum yield of the desired products were carefully worked out. The nature and scope of these experiments has been explored in the Discussion section but space limitations preclude a detailed description. Method A is recommended for compounds, which for steric reasons react too slowly or not at all with bromine. Method B is the most generally applicable method. Methods C and C′ were used with some success in those cases where the previous methods failed and are still in the development stage.

Method A. Phenyl Trityl Ketone from Tetraphenylethylene.—A chlorine cylinder was connected successively to an empty trap, a reaction flask, another empty trap, a trap containing water, and two traps containing a saturated solution of potassium carbonate. The reaction flask was equipped with a magnetic stirrer, a pressure addition funnel, and gas inlet tube with a fritted glass tip. Commercial grade (mp 220–223°) tetraphenylethylene (3.3. g, *ca.* 0.01 mol) was dissolved in chloroform (250 ml) and introduced to the reaction flask which was immersed in an ice bath. While the mixture was stirred chlorine gas was allowed to flow through at a slow rate until the solution had acquired a distinct yellow color. The flow of gas was then discontinued and the stirred mixture was treated all at once with a saturated silver nitrate solution (350 ml) made up with methanol (90% by volume) and water (10% by volume). The mixture was stirred at room temperature overnight, after which the inorganic salts were filtered off and washed with chloroform, and the washings and the filtrate were combined. An excess of water was then added to the filtrate and the chloroform layer was separated, washed several times with water, and dried over anhydrous magnesium and sodium sulfates. Upon removal of the solvents a viscous oil was obtained (3.27 g, 94%) which crystallized spontaneously.

The product was identified by its infrared and nmr spectra as phenyl trityl ketone.

After two recrystallizations from ethanol a pure (mp 183–184°) product (3 g, 86%) was obtained. Compound 2, Table I, was similarly treated.

Method B. Phenyl Benzhydryl Ketone from Triphenylethylene.—A sample (0.8832 g) of pure (mp 71–72°) triphenylethylene was dissolved in chloroform (25 ml) and cooled in a Dry Ice–isopropyl alcohol bath. The stirred reactants were then treated rapidly (*ca.* 1 min) with a bromine solution (5% Br_2 and 95% $CHCl_3$ by volume) until the first appearance of a permanent amber color.

Approximately 5 ml of the bromine solution was required. The mixture was then decomposed at *once* by the addition of a saturated silver nitrate solution (50 ml) made up with methanol (90% by volume) and water (10% by volume). After a work-up procedure identical with that given in method A, a quantitative yield of crude phenyl benzhydryl ketone was obtained. After two recrystallizations from methanol a pure (mp 138–139°) sample (0.8834 g, 94%) of phenyl benzhydryl ketone was obtained. Compounds 3–28, in Table I, were similarly treated with the results shown therein.

Method C. 2-Phenylpropionaldehyde from *trans*-1-Phenyl-1-propene.—A commercial[25] sample (1 ml, *ca.* 0.0076 mol) of *trans*-1-phenyl-1-propene was dissolved in chloroform (50 ml). The solution was stirred magnetically at room temperature and treated rapidly with bromine (*ca.* 0.5 ml) until the first appearance of a permanent amber color. The mixture was then immediately decomposed by the addition of silver carbonate–Celite reagent[6] (6 g). The heterogeneous mixture was stirred at room temperature for 2 days, during which the silver carbonate reagent became progressively darker. The phases were separated by filtration and the solid phase was washed several times with chloroform, combining the washings with the filtrate. After removal of the solvent by fractional distillation a residual oil (0.835 g, 82%) remained which was identified by its infrared and nmr spectra as 2-phenylpropionaldehyde. Compounds 30, 34, and 37, Table I, were similarly treated except that in the case of compound 34 the starting solution was the end product of an unsuccessful attempt to promote the rearrangement by method B.

Method C′. Methyl Isopropyl Ketone from 2-Methyl-2-butene.—A commercial[26] sample of 2-methyl-2-butene (1 ml, *ca.*

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[24] Professor M. Fétizon, Ecole Polytechnique, Paris, France.

[25] Fluka Chemical Co., Geneva, Switzerland.

[26] Prolabo Chemical Co., Paris, France.

0.0094 mol) dissolved in CCl_4 (50 ml) was brominated and decomposed as in method C. The heterogeneous mixture was then refluxed for 2 days, after which the supernatant liquid was examined by infrared, nmr, and gas chromatography. Comparison of these spectra with the corresponding spectra of an authentic sample revealed that the only carbonyl compound produced was methyl isopropyl ketone. The yield of the ketone (38%) was determined by integration of the gas chromatographic peaks. Compounds 31, 33, and 35–36, Table I, were similarly treated, with the results stated therein.

Registry No.—Phenyl trityl ketone, 466-37-5; tetraphenylethylene, 632-51-9; phenyl benzhydryl ketone, 1733-63-7; triphenylethylene, 58-72-0; 2-phenylpropionaldehyde, 93-53-8; *trans*-1-phenyl-1-propene, 873-66-5; methyl isopropyl ketone, 563-80-4; 2-methyl-2-butene, 513-35-9.

Acknowledgment.—We are indebted to Dr. Lloyd Snyder for taking the mass spectra, to Dr. C. J. Collins, B. Benjamin, and V. Raaen for their help in the synthesis and assay of the isotopically labeled compounds, and to Professor M. Fétizon for supplying us with some of the samples and reagents.

Notes

Synthesis of *dl*-Muscone from Exaltone (Cyclopentadecanone)

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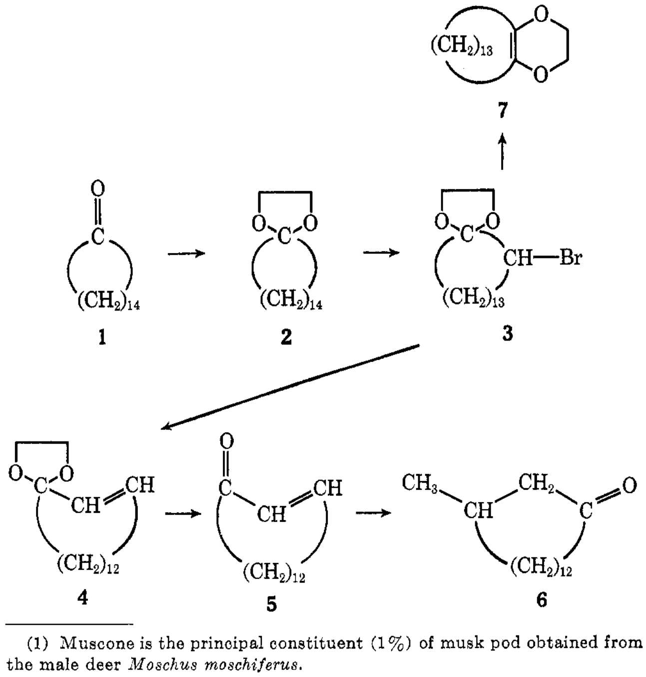
Muscone (6) and exaltone (1) are two similar compounds. The difference is that the former is a natural product;[1] the latter lacks a β-methyl group. Though there is a plethora of publications[2] for the synthesis of 6 from various starting materials, only Ruzicka and Stoll[3] have described the preparation of 6 from 1 in poor yield, The present paper reports an alternate five-step synthesis of *dl*-muscone (6) from exaltone (1) in an overall yield of 60%.



Treatment of 1 with ethylene glycol and *p*-toluenesulfonic acid monohydrate[4] in benzene afforded ketal 2 (98%) which was brominated with phenyltrimethylammonium tribromide[4,5] in tetrahydrofuran for 2 hr at 0° to give 2-bromo ketal 3 (≈100%). Though the treatment of 3 with potassium *tert*-butoxide in either *tert*-butyl alcohol or dimethyl sulfoxide[6] gave only dioxin 7, dehydrobromination of 3 with 1,5-diazabicyclo[4.3.0]non-5-ene[7,8] at 110° for 64 hr furnished the α,β-unsaturated ketal 4 (70%). Mild acid hydrolysis of 4 gave cyclopentadecenone (5) (100%) which on treatment with methyl Grignard in the presence of cuprous chloride and ether[2,9] was smoothly converted to *dl*-muscone (6) (81%).

Experimental Section

Melting points are uncorrected. Gas–liquid chromatography (glc) analyses were performed on an F & M 810 instrument using 5% Carbowax 20M and 5% silicone SE-30 coated on Anakrom ABS (80–100 mesh) packed in stainless steel columns (25 ft × 0.25 in.). The following spectrometers were used: infrared, Beckman IR-5A or Beckman IR-4; nuclear magnetic resonance, Varian HA-100 (CCl_4, TMS as internal standard); mass spectra, CEC Model 21-103 C, and AEI MS 9 for high-resolution spectra. Major mass spectral fragmentation peaks were recorded in decreasing order of intensity except for the molecular ion $(M)^+$ peak which is listed first. Five per cent deactivated silicic acid made by adding 5 ml of water to 95 g of silicic acid (Grace, 100–200 mesh) was used for column chromatography. Anhydrous magnesium sulfate was used as drying agent. Exaltone was purchased from Firmenich, New York, N. Y.

Ethylene Ketal of Cyclopentadecanone (2).—A mixture of 1 (50 g, 0.22 mol), *p*-toluenesulfonic acid monohydrate (4.2 g, 0.022 mol), freshly distilled ethylene glycol (444 ml), and anhydrous benzene (2.7 l.) was refluxed with constant removal of water. After 14 hr of reflux, 14 ml of water was collected. The mixture was cooled, the ethylene glycol layer was separated, and the benzene layer was washed successively with saturated sodium bicarbonate solution and sodium chloride solution and

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[1] Muscone is the principal constituent (1%) of musk pod obtained from the male deer *Moschus moschiferus*.

[2] B. D. Mookherjee, R. Trenkle, and R. R. Patel, *J. Org. Chem.*, **36**, 3266 (1971), and references cited therein.

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