Rearrangement of III to IV.—A solution of 300 mg. (0.87 mmole) of III in 1 g. of piperidine and 1.5 ml. of methanol was refluxed for 5 hr. Elimination of piperidine and methanol *in vacuo* followed by fractional crystallization of the oily residue from ethyl acetate afforded 40 mg. (13%) of IV.

Analogous treatment of IV resulted in total recovery of the starting material.

Acknowledgment.—We take pleasure in thanking Professor G. Berti for many helpful discussions.

Some Observations on Allylic Oxidation¹

KENNETH B. WIBERG² AND STUART D. NIELSEN³

Department of Chemistry, University of Washington Seattle, Washington

Received May 4, 1964

Allylic oxidation by mercuric acetate, lead tetraacetate, chromic acid, and selenium dioxide have been studied. The oxidation by the first two reagents involves a symmetrical intermediate which is probably formed via the decomposition of an allylmercuric or an allyllead intermediate. The oxidation by chromic acid also leads to a symmetrical intermediate. However, the difference in position of attack between this reagent and the other two suggests that it is the initial attack by chromic acid which forms the symmetrical intermediate. The oxidation by selenium dioxide differs from that of the other reagents in that asymmetry is retained during the reaction. The oxidation of (+)-carvomenthene in aqueous ethanol gave carvotanacetone with 45-55% retention of configuration (*i.e.*, attack at the allylic carbon), but the oxidation of cyclohexene-C¹³ gave 90\% reaction at the olefinic carbon. The mechanisms of the reactions are discussed.

Allylic oxidation by N-bromosuccinimide and related N-halo compounds has been extensively studied. The kinetics of the reaction with cyclohexene have been examined in detail,⁴ the stereochemistry⁵ and effect of substituents⁶ have been studied, and other aspects of the reaction have also been investigated.⁷ As a result, the nature of the reaction is fairly well understood. However, allylic oxidation by other reagents such as selenium dioxide,⁸ chromic acid,⁹ lead tetraacetate,¹⁰ and mercuric acetate¹¹ have received relatively little attention. Some experiments designed to give information on the nature of the intermediates involved are described below.

Mercuric Acetate.—The oxidation of (+)-carvomenthene (A) by mercuric acetate has been investigated by Treibs and Bast¹⁰ and by Kergomard.¹² The product was (\pm) -carvotanacetol acetate (B), which on hydrolysis and oxidation gave (\pm) -carvotanacetone. From this it was concluded that a sym-



(1) This work was supported by a grant from the National Science Foundation.

(2) To whom correspondence should be addressed at the Department of Chemistry, Yale University, New Haven, Conn.

(3) Taken from part of a thesis submitted to the University of Washington in partial fulfillment of the requirements for the Ph.D. degree, 1962; Allied Chemical Corp. Fellow, 1960-1961.

(4) H. J. Dauben, Jr., and E. A. Youngman, unpublished results, quoted in C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 382.

(5) H. J. Dauben, Jr., and L. L. McCoy, J. Am. Chem. Soc., 81, 5404 (1959).

(6) R. E. Pearson and J. C. Martin, *ibid.*, **85**, 354 (1963); G. A. Russell,
 C. De Boer, and K. M. Desmond, *ibid.*, **85**, 365 (1963).

(7) C. Walling, ref. 4, p. 381; H. J. Dauben, Jr., and L. L. McCoy, J. Am. Chem. Soc., 81, 4863 (1959).

(8) Cf. G. R. Waitkins and C. W. Clark, Chem. Rev., 36, 235 (1945).

(9) F. C. Whitmore and G. W. Pedlow, J. Am. Chem. Soc., 63, 758 (1941).

(10) R. Criegee, Ann., 481, 263 (1930).

(11) W. Treibs and H. Bast, *ibid.*, **561**, 165 (1949); W. Treibs, G. Lucius, H. Kögler and H. Breslauer, *ibid.*, **581**, 59 (1953).

(12) A. Kergomard, Ann. chim. (Paris), 8, 153 (1953).

metrical intermediate, presumably the allyl radical or cation, was involved as an intermediate.

It had not been established that the reactant and product are configurationally stable under the reaction conditions. In order to settle this point, in one experiment, we employed a 100% excess of (+)-carvomenthene and found that the recovered hydrocarbon had 99% of its original rotation. In a second run, a sample of (+)-carvotanacetol acetate was heated with mercuric acetate and acetic acid under the reaction conditions. The recovered acetate had 96% of its original rotation. To check the possibility that some intermediate catalyzed the racemization of the product, an amount of carvotanacetol acetate (αD 34.6°) equivalent to that expected as the product was added to the reactants, and the reaction was carried out as usual. The product had a rotation of αD 16.7° indicating no significant racemization of the product once it is formed.

It was possible to separate the two epimeric carvotanacetol acetates by gas chromatography. The ratio of *trans* to *cis* was 72:28.¹³

In order to be sure that the reaction would proceed on the same course with a less substituted alkene, we examined the oxidation of cyclohexene-C¹³. Starting with material having 1.442 - 0.004% C¹³ at each end of the double bond, the reaction was carried out to give 3-acetoxycyclohexene. Hydrogenation, hydrolysis and oxidation gave cyclohexanone, which was degraded by the method of Loftfield¹⁴ to give the carbonyl carbon in the form of carbon dioxide. Analysis of the latter indicated that the carbon attached to the acetoxy group had $1.268 \pm 0.018\%$ C¹³ (average of duplicate determinations) which is very close to that expected for a symmetrical intermediate (1.276%).¹⁵ These data confirm that a symmetrical intermediate is involved in the reaction.

The oxidation of 1-methylcyclohexene proceeds under the same conditions as for cyclohexene, and gives about

(13) The assignment of configuration of the carvotanacetols was based on the work of H. G. Kuivila and O. F. Beumell, Jr., J. Am. Chem. Soc., 83, 1246 (1961).

(14) R. B. Loftfield, ibid., 73, 4707 (1951).

(15) The normal abundance of carbon-13 was taken as $1.110\,\%$ and all data were normalized to this value.

the same yield of acetoxy-substituted product (21%)with the former and 19% with the latter) along with a considerable amount of recovered alkene. When a mixture of 1 equiv. of each of cyclohexene, methylcyclohexene, and mercuric acetate was heated, the ratio of acetates was 4:1, with that from 1-methylcyclohexene predominating. Similarly, the recovered hydrocarbon mixture contained cyclohexene and methylcyclohexene in a ratio of 2:1. Thus methyl substitution gave a small rate increase. The course of the oxidation is affected by methyl substitution. For example, the two isomeric *p*-menthenes are reported to give oxidation largely at the position α to the more substituted end of the double bond.¹¹



The addition of mercuric salts to alkenes occurs readily, and Kergomard¹² has suggested that the allylic oxidation occurs by way of this adduct. This appeared

$$C = C + HgX_2 \longrightarrow X - O - C - HgX$$

to be supported by our observation that, when a sealed tube containing the alkene and mercuric acetate was allowed to stand for a few days at room temperature, the adduct was formed, and this had no effect on the yield of product formed or on the stereochemistry of the reaction. However, when the adduct from cyclohexene was heated at the reaction temperature in an open tube, nearly pure cyclohexene distilled off. Thus, the equilibrium between the adduct and mercuric salt appears to be shifted toward the latter at higher temperatures, and the question of the adduct being an intermediate remains unanswered.

In order to determine something about the nature of the intermediate involved, it is interesting to examine the previously obtained data on the oxidation of α pinene. In aqueous solution, the product was sobrerol (C), and it is important to note that (+)- α -pinene gave (\pm) -sobrerol.¹⁶ The cleavage reaction cannot result from a hydrogen atom abstraction, but it may arise as a result of the addition of either a cation or a free radical to the double bond. Thus, for example, α -pinene is converted by acid-catalyzed hydration to α -terpineol¹⁷ and β -pinene is converted to 7-trichloromethyl-8chlorocarvomenthene by the free-radical catalyzed addition of carbon tetrachloride.¹⁸

When the oxidation was carried out in acetic acid as the solvent, the course was somewhat different and led to a mixture of about equal amounts of sobrerol diacetate (D), myrtenyl acetate (E), and pinocarvyl acetate (F).¹² Thus, complete rearrangement did not occur in this medium of low dielectric constant. In view of the similarity of the two reactions (*i.e.*, that leading to D and that leading to E and F) it is reasonable to suppose that the mechanisms are related.



The data are reasonably interpreted as involving the addition of the mercuriacetate cation to the double bond leading to a mercurinium ion as an intermediate.¹⁹ The ion may be partitioned between addition of acetate ion, giving the adduct mentioned above, and elimination of a proton, giving the substituted allylmercuriacetate. The reaction in water might reasonably be expected to proceed *via* the carbonium ion, leading to ring cleavage in the case of α -pinene. In the solvent of lower dielectric constant, acetic acid, acetate ion may participate in the reaction of the mercurinium ion and thereby lead to 3-acetoxymercuri- β -pinene.

The allylmercuriacetate would be expected to decompose under the reaction conditions,²⁰ and it is at this stage that the symmetrical intermediate is probably formed. If the decomposition follows an ionic path, as is likely, the results of Goering and Silversmith²¹ on the solvolysis of cyclohexen-3-ol derivatives indicate that the resulting product should be racemic. The reaction sequence, in the case of α -pinene, appears to be the following.



 ⁽¹⁶⁾ G. G. Henderson and J. W. Agnew, J. Chem. Soc., 95, 289 (1909);
 G. G. Henderson and J. W. S. Eastburn, *ibid.*, 95, 1465 (1909).

⁽¹⁷⁾ P. Barbier and V. Grignard, Bull. soc. chim. France, [4] 5, 512, 519 (1909); F. G. Germuth, Am. J. Pharm., 99, 402 (1927).

⁽¹⁸⁾ D. M. Oldroyd, G. S. Fisher, and L. A. Goldblatt, J. Am. Chem. Soc., 72, 2407 (1950).

This mechanism accounts for the formation of racemic carvotanacetol acetate from optically active carvomenthene and for the formation of products in which the acetoxy group is adjacent to the more substituted end of the double bond. It will also account for the fact that a methyl group gives only a small accelerating effect. The rate-determining step is not the formation of the mercurinium ion since the addition of mercuric acetate occurs at room temperature, whereas the oxidation occurs at a reasonable rate only at a temperature in the vicinity of 160°. Rather, it is probably the step in which the all vlmer curiacetate is formed. The methyl group stabilizes the double bond in the alkene and the incipient double bond in the activated complex. Thus the effect of the methyl group in the reactant and activated complex may roughly cancel leading to only a small net effect.

It should be recognized that the above mechanism is analogous to that for mercuric acetate dehydrogenation of steroids proposed by Barton and Rosenfelder,²² and by Ruyle, *et al.*,²³ and is similar to that proposed by Kergomard.¹²

Lead Tetraacetate.—The oxidation of (+)-carvomenthene has been studied by Kergomard,¹² and by Aratani²⁴ who found the products to be carvotanacetol acetate and p-menthane-1,2-diol diacetate. The former was racemic. We have examined the possibility of racemization of reactant and/or product under the reaction conditions in the same way as for the mercuric acetate oxidation and no significant racemization was observed. Thus, again, a symmetrical intermediate appears to be involved. This was confirmed using cyclohexene-C¹³ which gave 3-acetoxycyclohexene having $1.274 \pm 0.006\%$ C¹³ at the carbon holding the acetoxy group when the reaction was carried out in benzene and $1.290 \pm 0.004\%$ C¹³ when it was carried out in acetic acid solution. The formation of a symmetrical intermediate should lead to 1.276% C¹³, whereas specific attack at the olefinic carbon or at the allylic carbon should lead to 1.442 and 1.110%, respectively.

The lead tetraacetate oxidation is, however, not so clean as the mercuric acetate oxidation. When the reaction was carried out in benzene, the product was a mixture of 17 components including 11% unchanged hydrocarbon and 12.5% carvotanacetol acetates in the proportion 68% cis and 32% trans. Fewer products were found when acetic acid was used ε s the solvent, and the carvotanacetol acetates were obtained in 17% yield with an isomer distribution of 40% cis and 60% trans. The following discussion will be limited to that part of the reaction which leads to the allylic acetates.

As with the mercuric acetate oxidation, cyclohexene and 1-methylcyclohexene were oxidized under similar conditions to give equal yields of acetates (25% from the former and 24% from the latter). The reaction of an equimolar mixture of the two alkenes with lead tetraacetate in benzene gave the acetates in the ratio

D. W. Rosenberg, G. E. Sika, R. B. 1968501, D. M. Amminiosa, and M. Tishler, J. Am. Chem. Soc., **75**, 2604 (1953).

(24) T. Aratani, Nippon Kagaku Zasshi, 78, 1534 (1957); Chem. Abstr., 54, 1587 (1960).

2.5:1, with that from methylcyclohexene predominating. Thus, methyl substitution led to a small rate increase.

The oxidation of α -pinene has been studied by Whitham²⁵ in benzene solution, and by Criegee²⁶ in an acetic acid solution. In benzene, the product was *cis*-2acetoxypin-3-ene (G), which in the presence of acetic acid was rapidly rearranged to *trans*-verbenyl acetate (H). In acetic acid, the products were verbenyl acetate and (±)-sobrerol diacetate (I).



These results again suggest that an ionic addition is involved. It would be difficult, for example, to explain the formation of 2-acetoxypin-3-ene by any free-radical abstraction mechanism and the effect of solvent on product composition is in better accord with an ionic addition mechanism than with one involving free-radical additions. The first step probably invites the addition of either the acetoxy cation or the lead triacetate cation. The former was suggested by Brutcher and Vara²⁷ as a result of their observations on the reaction of lead tetraacetate with cyclopentadiene. However, the results obtained by Criegee, et al., on the reaction of styrene and p-methoxystyrene with lead tetraacetate is more satisfactorily accommodated if one assumes that the lead triacetate cation is the addend.²⁸ The results of Brutcher and Vara are also readily explained if one assumes initial addition of this cation.

As a result of his observation that α -pinene gave *cis*-2acetoxypin-3-ene, Whitham proposed the following mechanism and suggested that a similar process may be



involved in the allylic oxidation of other alkenes. With cyclohexene, the sequence might be the following.



⁽²⁵⁾ G. H. Whitham, J. Chem. Soc., 2232 (1961).

 ⁽¹⁹⁾ H. J. Lucas, F. R. Hepner, and S. Winstein, J. Am. Chem. Soc., 61,
 3102 (1939); M. J. S. Dewar, Bull. soc. chim. France. 18, C79 (1951).

⁽²⁰⁾ D. J. Foster and E. Tobler, J. Org. Chem., 27, 834 (1962).

⁽²¹⁾ H. L. Goering and E. F. Silversmith, J. Am. Chem. Soc., 77, 6249 (1955).

⁽²²⁾ D. H. R. Barton and W. J. Rosenfelder, J. Chem. Soc., 2381 (1951).
(23) W. V. Ruyle, J. A. Jacobs, J. M. Chemerda, E. M. Chaimberlain, D. W. Rosenberg, G. E. Sita, R. L. Erickson, L. M. Aliminosa, and M.

⁽²⁶⁾ R. Criegee, Angew. Chem., 70, 173 (1958).

⁽²⁷⁾ F. V. Brutcher and F. J. Vara, J. Am. Chem. Soc., 78, 5696 (1956).

⁽²⁸⁾ R. Criegee, P. Dimroth, K. Noll, R. Simon, and C. Weis, Ber., 90, 1070 (1957).

However, this is not in accord with the present observation that a symmetrical intermediate is involved both in the oxidation of carvomenthene and of cyclohexene.

It is still reasonable to suppose that the normal course of the reaction involves the addition of the lead triacetate cation. The product in the case of cyclohexene and carvomethane, may be formed by the elimination of a proton and a subsequent reaction of the allyl lead compound.²⁹ We have chosen to write the addition of



 $Pb(OAc)_{3}^{+}$ as an equilibrium reaction in order to account for the small effect on the rate of reaction of a methyl group attached to the double bond, which is similar to that observed in the mercuric acetate oxidation. It would be reasonable to expect that, if the addition of the lead triacetate cation were rate determining, a larger rate difference would be found. Whether or not the addition of acetate ion to the intermediate, giving the compound which ultimately leads to the *trans* diacetate in dry acetic acid, is reversible or not remains to be determined.

Chromic Acid.—The chromic acid oxidation of cyclohexene leads to two products, adipic acid and cyclohexenone.⁹ If one were to assume that the two reactions involved a common intermediate, then one would suppose the initial step involved the addition of chromic acid to the double bond. However, the fact that the oxidation of α -pinene gives verbenone,^{30,31} which is similar to the reaction with N-bromosuccinimide³² and to autoxidation,³³ makes this appear unlikely.



Cyclohexene-C¹³ was oxidized with chromic acid, and the cyclohexenone was degraded by the procedure described above. The carbonyl carbon was found to have $1.223 \pm 0.004\%$ C¹³ when the cyclohexene had $1.332 \pm 0.004\%$ C¹³ at each of the olefinic carbons. This indi-

(29) R. Criegee, P. Dimroth, and R. Schempf, Ber., **90**, 1337 (1957) have presented evidence indicating that the organolead intermediate would be unstable and would decompose to Pb(II) and a cation.

(30) W. Treibs and H. Schmidt, *ibid.*, **61**, 459 (1928). See also T. Matsumura and K. Fujita, J. Sci. Hiroshima Univ., **16A**, 173 (1952).

(31) G. Dupont, R. Dolou, and O. Mondou, Bull. soc. chim. France, 60 (1953).

(32) Buu-Hoi, Hoing-Ki-Wei, L. Lecomte, and R. Roger, *ibid.*, 148 (1946).

(33) A. Blumann and O. Zeitschel, Ber., 46, 1178 (1913).

cates the formation of a symmetrical intermediate for which 1.221% C¹³ would have been expected at the carbonyl carbon.

The oxidation of 1-methylcyclohexene led to 2methylcyclohex-3-one (20%) and 1-methylcyclohexen-3-one (6%).⁹ This result is quite different from that found in mercuric acetate oxidation where 1-methylcyclohexene gave only 2-methylcyclohex-2-enyl acetate. Similarly, the oxidation of carvomenthene by *t*-butyl chromate, which is similar to chromic acid in most of its reactions, gave carvotanacetone (J) and piperitone (K) in equal amounts.³¹ The mercuric ace-



tate and lead tetraacetate oxidations gave only carvotanacetol acetate.

The observations discussed above indicate a fundamental difference between allylic oxidation by chromic acid on one hand, and oxidation by mercuric acetate and by lead tetraacetate on the other. They suggest that the symmetrical intermediate is formed in the initial step rather than in a later stage in the reaction. The obvious possibilities are hydrogen atom or hydride ion abstraction from the allylic position leading to the allyl radical or cation. It is difficult to distinguish between these possibilities; our previous conclusions concerning chromic acid and chromyl chloride oxidation of hydrocarbons lead us to suggest that the reaction is a hydrogen atom abstraction. It is not possible to speculate on the nature of the subsequent steps in view of the limited amount of data which are available.

Selenium Dioxide.—The reaction of selenium dioxide with alkenes leads to oxidation at the allylic position. The product is a function of the solvent.⁸⁴ In acetic acid, the acetate is formed; in ethanol one obtains the ether; and in water the product is usually the α,β -unsaturated ketone which probably arises from the oxidation of the alcohol first formed. As a result of the work of Guillemonat,³⁵ one may predict the course of the selenium dioxide oxidation of alkenes based on the following rules.

(1) The oxidation always occurs α to the most substituted end of the double bond.

(2) When the double bond is in a ring, whenever possible, oxidation occurs within the ring.

(3) The order of preference for oxidation is $CH_2 > CH_3 > CH$.

(4) When the double bond is terminal, rather than the expected secondary alcohol or derivative thereof, the primary alcohol is formed with the migration of the double bond.

Because of the similarity in selectivity between the reactions of selenium dioxide and that of reagents such as N-bromosuccinimide, Waters,³⁶ and Campbell, Walker, and Coppinger³⁷ suggested that the reaction

(34) K. Alder and G. Stern, Ann., 504, 205 (1933).

(35) A. Guillemonat, Compt. rend., 200, 1416 (1935); 201, 904 (1935);
 205, 67 (1937); 206, 1126 (1938); Ann. chim. (Paris), 11, 143 (1939).

(36) W. A. Waters, J. Chem. Soc., 1805 (1939).

(37) T. W. Campbell, H. G. Walker, and G. M. Coppinger, Chem. Rev: 50, 279 (1952).

proceeded via a hydrogen atom abstraction from the alkene. We were led to question this view since the oxidation of α -pinene by N-bromosuccinimide^{32,38} and by selenium dioxide³⁹ appears to lead to different positions of attack.



A simple way in which to test the possibility of forming a free radical intermediate is to determine whether or not a symmetrical intermediate is formed in the oxidation of a compound such as (+)-carvomenthene. An intermediate of this type would lead to a racemic oxidation product. Although the selenium dioxide oxidation of carvomenthene has been reported several times,⁴⁰ in no case was the rotation of the product carvotanacetone reported.⁴¹ Starting with (+)-carvomenthene, having 94% optical purity, we found the product of the oxidation in aqueous ethanol to be (+)-carvotanacetone (J) having a rotation between $[\alpha]D + 24.5$ and 30.6° (several runs) which corresponds to 44-55% retention of asymmetry. Only one other carbonyl-con-



taining compound was found, and this was identified as phellandral (L). Gas chromatographic analysis failed to show the presence of any piperitone (K).



The relative configuration of (+)-carvomenthene and (+)-carvotanacetone is now of interest in order to determine whether the reaction proceeds with retention or inversion of configuration. (+)-Limonene reacts with nitrosyl chloride to give the nitrosochloride. The latter, on treatment with base, gave an oxime which was identical with (-)-carvoxime.⁴² (+)-Limonene on hydro-



genation gave (+)-carvomenthene, and (+)-carvone on hydrogenation gave (+)-carvotanacetone. It is difficult to imagine any other course for the series of reactions given above, and, since they involve an effective inversion of configuration (*i.e.*, movement of the double bond), it appears that (+)-carvomenthene is related to (+)-carvotanacetone.

The same conclusion may be reached using a different series of reactions. (+)-Limonene has been converted to the monoepoxide, and then to the diol. In one set of reactions, the diol was oxidized to the ketol and dehydrated giving (-)-carvone. In another, the diol was converted to the diacetate, followed by elimination of acetic acid. The resulting acetate was hydrolyzed and oxidized to (-)-carvone.⁴³



The observation of predominant retention of configuration in the selenium dioxide oxidation permits only two types of mechanisms, a direct insertion reaction (or its two-step cage equivalent)⁴⁴ at the methylene position, and an addition-elimination mechanism of the type described below. The former possibility appears unlikely for the following reasons. First, it would be difficult to explain the important role of the disubstituted end of the double bond on this basis, and second, it would not explain the course of reaction with terminal double bonds in which an allylic shift is observed.

The other possibility may be formulated as follows. Selenium dioxide exists as selenous acid in a solvent containing water. It is reasonable to assume that in the acidic medium, the selenous acid is protonated to give the equilibrium concentration of the conjugate acid.⁴⁵ This may be in the form of $H_3SeO_3^+$ or $HSeO_2^+$. The exact form is not known, and it will be written as the latter for convenience. Addition of $HSeO_2^+$ to the

(44) K. B. Wiberg and G. Foster, J. Am. Chem. Soc., 83, 423 (1961).

⁽³⁸⁾ Autoxidation occurs at the same position as the N-bromosuccinimide reaction.²³

⁽³⁹⁾ G. Dupont and W. Zacharewicz, Bull. soc. chim. France, [5] 2, 533 (1935).

⁽⁴⁰⁾ J. Allard, Thesis, Bordeaux, 1933; E. Borgwardt and E. Schwenk, J. Am. Chem. Soc., 56, 1185 (1934); J. Tabuteau, Compt. rend., 200, 244 (1935).

⁽⁴¹⁾ After this work was completed, the oxidation of carvomenthene in wet dioxane to carvotanacetone having a small rotation was reported by C. H. Nelson and E. N. Trachtenberg, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962, p. 78Q. In acetic acid-acetic anhydride solvent, they found only racemic carvomenthenolacetate.

⁽⁴²⁾ H. Goldschmidt and R. Zurrer, Ber., 18, 2220 (1885); E. E. Royals and S. E. Horne, Jr., J. Am. Chem. Soc., 73, 5856 (1951); C. Bordenca, R. K. Allison, and P. H. Dirstine, Ind. Eng. Chem., 43, 1196 (1951). Cf. A. J. Birch, Ann. Rept. Chem. Soc., 192 (1950), and K. Freudenberg and W. Lwowski, Ann., 587, 213 (1954), for a summary of the configurations of terpenes and related compounds.

⁽⁴³⁾ S. M. Linder and F. P. Greenspan, J. Org. Chem., 22, 949 (1957).

⁽⁴⁵⁾ Cf. E. J. Corey and J. P. Schaefer, ibid., 82, 918 (1960).

double bond would be expected in the normal direction, leading to an intermediate having the selenium function at the less substituted end of the double bond.

After the addition, proton loss may occur to give substituted alkenes, and this would follow the usual rule giving largely the endocyclic double bond in the cyclohexane series. There are several possibilities for the next reaction. First, there may be a competition between an SN2' and an SN2 displacement by the solvent giving over-all retention of configuration in the former case and over-all inversion in the latter. An SN2' displacement would account for the product and predominant stereochemistry observed in most cases, but with the terminal alkenes, the SN2 process would have to predominate, as might be expected on steric grounds.



Another possibility is that the competition is between an Sn2' and an Sn1 process, where the latter would lead to the symmetrical allyl cation, and this in turn would lead to a racemic product. This formulation has the advantage that it would explain the much lower degree of retention of asymmetry found in acetic acid or in moist dioxane.⁴¹ In a solvent having a lower nucleophilicity than aqueous ethanol, the Sn2' process would not be expected to be important, and the Sn1 path would be expected to predominate. A low degree of retention of asymmetry might also be anticipated if the allyl cation which could be formed had additional stabilization by electron-releasing groups.

The mechanistic hypothesis also explains the formation of selenium-containing products arising from 2 moles of hydrocarbon and 1 mole of selenium dioxide. The allyl seleninic acid intermediate could react with another mole of alkene in the same fashion as in the initial reaction.

The case of cyclohexene is interesting in that the yield of cyclohexenyl acetate is very low, and the major product is a selenium-containing compound. As has been noted previously,³⁷ this material, on pyrolysis, gives cyclohexenyl acetate. In order to determine something about the nature of the selenium-containing intermediate, the reaction was carried out using cyclohexene labeled with C¹³ at the double bond. The carbon holding the acetoxy group was found to have 1.405% C¹³ as compared with 1.442% at each end of the double

bond in the cyclohexene, indicating that the acetoxy group was introduced at one of the original olefinic carbons 90% of the time.

The selenium-containing compound was shown to contain oxygen by elemental analysis, and the presence of an acetoxy group was indicated by both the infrared and the n.m.r. spectra. The data then permit two types of structures for the intermediate. The first



structure would be formed by the addition of acetate ion to the initial addition product, rather than elimination of a proton. Then an ester pyrolysis step involving the SeO group would give the product with the correct C^{13} distribution. In the other possibility, the acetoxy groups are attached to the selenium, and are transferred to the adjacent carbon in a cyclic mechanism during the pyrolysis step. The latter seems the less likely possibility since the acetoxy groups remain even when the intermediate is treated with water.

The results of Mousseron and Jacquier⁴⁶ on the selenium dioxide oxidation of (+)-4-methylcyclohexene in an acetic anhydride-acetic acid solvent are of interest in connection with the oxidation of cyclohexene. A major product was 5-methyl-2-cyclohexen-2-yl acetate. Hydrolysis, oxidation of the secondary alcohol function, and hydrogenation gave (-)-3-methylcyclohexanone with about 85% retention of asymmetry. The starting alkene was prepared by the reduction of (+)-3-methylcyclohexanone followed by dehydration⁴⁷ indicating that the entire sequence was effected with net inversion of configuration.



It is apparent that the reaction proceeded with the same stereochemical result as found with carvomenthene, and thus with a different course than found with cyclohexene. However, it is not clear from the experimental data what proportion of the product arose from the reaction in solution, and from the pyrolysis of the selenium-containing residues. Our data suggest that a different stereochemistry should be found for the two reactions. It is also interesting to note⁴¹ that the oxidation of carvomenthene in acetic acid gave an essentially racemic product, whereas Mousseron and Jaquier found

⁽⁴⁶⁾ M. Mousseron and R. Jaquier, Bull. soc. chim. France, 467 (1952).

⁽⁴⁷⁾ M. Mousseron, R. Richard, and R. Granger, ibid., 222 (1946).

high retention of asymmetry in this solvent. It would appear that a reinvestigation of the oxidation of 4methylcyclohexene will be required.

Although the mechanism of the selenium dioxide oxidation given above seems to explain most of the observations concerning the reaction, it may not be satisfactory when one considers the case of α -pinene. Here, the oxidation products are myrtenol and myrtenal. If a carbonium ion were developed adjacent to



the cyclobutane ring, one might expect either ring cleavage or rearrangement.⁴⁸ Since the amount of cleavage or rearrangement products appear to be negligible, serious doubt is cast on the initial step. If one accepts the general idea of an allylseleninic acid being an intermediate, one may consider the possible modes by which it may be formed. First, one may take the extreme view that the addition involves the formation of a free-radical intermediate rather than a cation. This appears unlikely because of the similarity with mercuric acetate and lead tetraacetate oxidations which almost certainly involve an ionic intermediate.

Another possibility is that the addition of selenous acid and the loss of a proton may be synchronous, thereby preventing ring cleavage or rearrangement. The third, and possibly most reasonable possibility, is that the rearrangement or ring cleavage observed with α -pinene is actually not very facile since the carbonium ion is tertiary,⁴⁹ and that the commonly observed reactions may involve conditions under which the carbonium ion may be reformed many times for each rearrangement or ring cleavage step. This is supported by the observation that the addition of hydrogen chloride to α -pinene at -50° gives the unrearranged chloride.⁵⁰ Then, one may propose that the initial reaction involves the addition of SeO_2H^+ to the double bond to give an intermediate similar to a bromonium ion. If one center is tertiary, this may go directly to the allylseleninic acid by the loss of a proton, and if no tertiary center is present and the loss of a proton is less facile, it may add acetate ion to give the β -acetoxyseleninic acid. It is



apparent that the data are not adequate to completely specify the mechanism, but the general course seems fairly clear.

Experimental⁵¹

Oxidizing Agents.—Selenium dioxide was always prepared immediately before use by the reaction of selenium with nitric acid. It was then sublimed at atmospheric pressure. Mercuric acetate was reagent grade and was not further purified. Lead tetraacetate was recrystallized from glacial acetic acid and dried in a vacuum desiccator immediately before use. Chromium trioxide was reagent grade.

(+)-Carvomenthene.—The hydrogenation of 100 ml. (84.2 g.) of (+)-limonene, αD +99.6°, was effected using 0.2 g. of platinum oxide catalyst and 30 p.s.i. of hydrogen. After 1 equiv. of hydrogen had been taken up, the reaction was stopped and the material was filtered and distilled through a 38-plate spinning-band column. The material having b.p. 176-178.5° was collected in several fractions having 87-97% carvomenthene, the rest being limonene and *p*-menthane. The pure carvomenthene was calculated to have a rotation, αD 89.3°.

(+)-Carvotanacetone.—The hydrogenation of 50 g. of (+)carvone was effected as above. Distillation gave 46 g. (91%) of (+)-carvotanacetone, b.p. 91–93° at 7–8 mm., αD +44.9°. Gas chromatographic analysis indicated the presence of 9% carvomenthone.

Reduction with lithium aluminum hydride gave a mixture of the (+)-carvotanacetols (αD + 24.1°), containing 89.5% of one isomer.

Cyclohexanone-1-C¹³.—A Grignard reagent was prepared from 10.0 g. (0.41 g.-atom) of magnesium and 46.0 ml. (0.20 mole) of 1,5-dibromopentane in 200 ml. of dry ether. An additional 800 ml. of ether was added, and carbon dioxide (66.4% C¹³), generated by the reaction of barium carbonate-C¹³ with 40% perchloric acid, was introduced by means of a tube dipping below the surface of the solution. The solution was allowed to stand overnight.

After treatment with 50 ml. of 6 N sulfuric acid and 200 ml. of water, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic solution was dried over magnesium sulfate, concentrated using a rotary evaporator, and distilled giving 2.1 g. (21%) of cyclohexanone-C¹³, b.p. 152-157°, and 5.68 g. of polymeric material.

The cyclohexanone was mixed with 2.1 g. of the ketone prepared in a previous run, and diluted with 114 g. of unlabeled cyclohexanone.

Cyclohexene-1-C¹³.—To 8.0 g. of lithium aluminum hydride in 250 ml. of dry ether was added dropwise with stirring 47.4 g. of cyclohexanone-1-C¹³ in 150 ml. of dry ether. After 1 hr., it was decomposed with 40% Rochelle salt solution. The ether solution was decanted, and the residue was washed with ether. Distillation gave 46.5 g. of cyclohexanol-C¹³ (96%).

A solution of 76.2 g. of cyclohexanol-C¹³ in 88 g. of pyridine was cooled in an ice bath. Ethyl chlorocarbonate, 113.5 g., was added dropwise with stirring. After the addition had been completed, the mixture was allowed to warm to room temperature and was stirred for an additional 6 hr. Water (75 ml.) was added and the mixture was extracted three times with ether. The ether solution was dried with sodium sulfate, concentrated using a rotary evaporator, and distilled giving 74 g. of ethyl cyclohexyl-1-C¹³ carbonate and 43 g. of a mixture of diethyl pyrocarbonate and ethyl cyclohexyl carbonate. Saponification of the latter mixture with methanolic potassium hydroxide gave 12.6 g. of cyclohexanol. The carbonate was formed in 80% yield based on the cyclohexanol consumed.

The carbonate was dropped at a rate of 2-3 drops/min. through a tube packed with $^{1}/_{16}$ -in. glass helices and heated to 450° in a Fisher microcombustion furnace. A slow stream of nitrogen was passed through during the pyrolysis. The products were collected in a Dry Ice-acetone cooled trap. The cyclohexene was isolated by preparative-scale gas chromatography (65% yield).

Isotopic Analysis for Cyclohexene.—A solution of 0.64 g. cyclohexene-1-C¹³ in 30 ml. of dry methanol was cooled in a Dry Ice-acetone cooled bath and treated with ozone until a deep blue color persisted. The solvent was removed under reduced pressure, and the residue was dissolved in 15 ml. of 90% formic acid. The addition of 8.5 ml. of 30% hydrogen peroxide followed by gentle warming led to a very vigorous reaction. After the spontaneous reaction had ceased, the mixture was heated to reflux for 30 min. The volatile materials were evaporated on a steam bath

⁽⁴⁸⁾ M. Berthelot, Ann., **110**, 367 (1859); Compt. rend., **55**, 496 (1862). (49) In this connection, one may note that, whereas the solvolytic reactions of cyclopropyl carbinol lead to ring-opened and rearranged products, this is not the case with the cyclopropyldialkylcarbinols.

⁽⁵⁰⁾ H. Meerwein and K. V. Emster, Ber., 55, 2521 (1922); H. Meerwein and J. Vorster, J. prakt. Chem., [2] 147, 83 (1936).

⁽⁵¹⁾ All rotations were determined neat in 1-dm. tubes.

using a stream of dry air. The residue was recrystallized from water giving 0.85 g. (75%) of adipic acid, m.p. $149.5-151^{\circ}$.

The adipic acid (0.25 g.) was dissolved in 3 ml. of concentrated sulfuric acid and 3 ml. of a benzene solution of hydrazoic acid (0.00613 mole) was added. The gas evolved was carried by a stream of helium through a Dry Ice cooled trap to remove benzene, and then through a liquid nitrogen cooled trap. The carbon dioxide was analyzed mass spectrometrically and the value was normalized to 1.100% normal abundance for tank carbon dioxide.

Degradation of 3-Acetoxycyclohexene-C13.-The 3-acetoxyevclohexene obtained from an oxidation (about 1 g.) was dissolved in 10 ml. of 95% ethanol and hydrogenated using platinum oxide catalyst. The solution was filtered and 1.5 g. of potassium hydroxide was added. After heating to reflux for 0.5 hr., the solution was poured into 10 ml. of saturated sodium chloride solution and extracted with several portions of ether. The ether solution was dried over anhydrous sodium sulfate and distilled giving cyclohexanol-C¹³. The latter was combined with a solution of 1.0 g. of potassium dichromate dihydrate and 0.5 ml. of concentrated sulfuric acid in 5 ml. of water. When the reaction had ceased, the excess oxidant was destroyed with methanol. The solution was saturated with sodium chloride and extracted with pentane. The pentane solution was dried over sodium sulfate and distilled giving cyclohexanone-C13. The latter was degraded by the method of Loftfield.¹⁴

Reaction of (+)-Carvomenthene with Mercuric Acetate.— Carvomenthene (5 g., 36.2 mmoles, αD + 91.7°) and 11.6 g. (36.2 mmoles) of mercuric acetate were sealed in a glass tube and heated at 140° for 2.5 hr. The tube was cooled and opened. The contents of the tube were filtered and dissolved in ether. The ether solution was washed with dilute sodium bicarbonate solution and with water, and was dried over anhydrous sodium sulfate. Distillation gave 1.9 g. of carvomenthene, 2.8 g. of carvotaneacetol acetate (b.p. 98-101° at 7 mm., αD +0.72°), and 1.45 g. of residue.

The carvotanacetol acetate was hydrolyzed and oxidized using the procedure given above for cyclohexyl acetate giving 1.2 g. of carvotanacetone, b.p. $124-127^{\circ}$ at 13 mm., $\alpha D 0.0^{\circ}$.

The reaction was repeated using a twofold excess of carvomenthene, $\alpha D 89.4^{\circ}$. The recovered carvomenthene had $\alpha D 88.1^{\circ}$. It was again repeated using equimolar quantities (2.5 g. of carvomenthene and 6.0 g. of mercuric acetate), but with 3.55 g. of carvotanacetol acetate added ($\alpha D + 34.6^{\circ}$). The carvotanacetol acetate which was isolated (4.6 g.) had $\alpha D 16.7^{\circ}$.

Reaction of Cyclohexene-1-C¹³ with Mercuric Acetate.—Cyclohexene-1-C¹³ (4.05 g., 49.3 mmoles) and mercuric acetate (15.0 g., 47 mmoles) were sealed in a glsss tube and heated at 160° for 4 hr. The tube was cooled and opened, and the organic phase was separated from the mercury (8.0 g., 85%). Distillation gave 2.9 g. of a mixture of acetic acid and recovered cyclohexene (2.0 g.), 3.0 g. (46%) of 3-acetoxycyclohexene (b.p. 128–132°), and 0.78 g. of residue. Another run on twice the scale gave 53% cyclohexene and 19% 3-acetoxycyclohexene.

Preparation and Pyrolysis of 2-Acetoxycyclohexylmercuriacetate.—A mixture of 32.0 g. (0.103 mole) of mercuric acetate and 8.1 g. (0.1 mole) of cyclohexene was placed in a flask and allowed to stand at room temperature for 2 weeks. The solid was broken up and transferred to a distilling flask which was then heated in a wax bath at 150°. A colorless liquid distilled over. Redistillation gave 4.9 g. (62% recovery) of cyclohexene and 0.7 g. (5%) of acetic acid. Extraction of the pot residue with ether followed by distillation gave 0.6 g. (5%) of 3-acetoxycyclohexene, b.p. 70–75° at 10 mm.

Reaction of 1-Methylcyclohexene with Mercuric Acetate.—A mixture of 13.4 g. (42 mmoles) of mercuric acetate and 4.07 g. (42 mmoles) of 1-methylcyclohexene was sealed in a glass tube and heated at 160° for 7 hr. The tube was opened and the contents were poured into 10 ml. of water. Mercury was separated from the mixture in quantitative yield. The reaction mixture was extracted with ether. The ether solution was washed with diluted sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated using a rotary evaporator. The residue was distilled to give 0.6 g. of 1-methylcyclohexene, 1.38 g. of 6-acetoxy-1-methylcyclohexene (21%), b.p. 73-78° at 10 mm.), and 0.4 g. of a material b.p. 110-120° at 10 mm., with an infrared spectrum almost identical with 6-acetoxy-1-methylcyclohexene.

Competitive Oxidation of Cyclohexene and 1-Methylcyclohexene by Mercuric Acetate.—A mixture of 16.0 g. (50.2 mmoles) of mercuric acetate, 4.1 g. (50 mmoles) of cyclohexene, and 4.8 g. (50 mmoles) of 1-methylcyclohexene was sealed in a glass tube and heated at 160° for 3.5 hr. The tube was cooled and opened, and the contents were poured into a mixture of 25 ml. of ether and 25 ml. of water. The ether solution was washed twice with sodium bicarbonate and with water, dried over anhydrous sodium

dium bicarbonate and with water, dried over anhydrous sodium sulfate, and concentrated using a rotary evaporator. Distillation of the residue gave 3.1 g. of recovered starting material, b.p. $75-107^{\circ}$, and 4.4 g. of acetates, b.p. $78-86^{\circ}$ at 10 mm. Gas chromatographic analysis of the first fraction indicated 63% cyclohexene and 37% 1-methylcyclohexene. Analysis of the second fraction indicated 82% 6-acetoxy-1-methylcyclohexene and 18% 3-acetoxycyclohexene.

Reaction of (+)-Carvomenthene with Lead Tetraacetate in Benzene.—A solution of 13.6 g. (30.7 mmoles) of lead tetraacetate and 4.3 g. (31.0 mmoles) of (+)-carvomenthene, αp +91.7°, in 55 ml. of benzene was heated to reflux for 8 hr. The mixture was cooled and filtered giving 8.4 g. (84%) of lead diacetate. The filtrate was poured into 50 ml. of water and filtered to remove lead dioxide. The filtrate was extracted with sodium bicarbonate solution, dried over sodium sulfate, and concentrated by distillation.

The crude acetate was hydrolyzed and oxidized with chromic acid as described above. Distillation gave 1.5 g. of carvotan-acetone, b.p. 80-88° at 6 mm. After purification by gas chromatography, it had $\alpha D 0.0^{\circ}$.

Reaction of Lead Tetraacetate with Excess (+)-Carvomenthene in Benzene.—The reaction was carried out as described above using 10.5 g. (23.7 mmoles) of lead tetraacetate, 8.6 g. (62.3 mmoles) of (+)-carvomenthene, and 75 ml. of benzene. The reaction product was distilled giving 5.6 g. of recovered starting material (b.p. 64-68° at 12 mm., αD +90.7°), 1.61 g. of acetates (b.p. 90-115°), and 1.67 g. of residue. The acetate mixture was found by gas chromatography to be a mixture of 17 components including 1.6% starting material, and 36% (12.5% yield) carvotanacetol acetates with an isomer ratio of 68% cis to 32% trans.

Reaction of Lead Tetraacetate with Excess (+)-Carvomenthene in Acetic Acid.—To a solution of 13.0 g. (29.3 mmoles) of lead tetraacetate in 50 ml. of glacial acetic acid was added 8.6 g. (62.3 mmoles) of (+)-carvomenthene, αD +89.4°. The mixture was heated on a steam bath for 4 hr. The reaction mixture was poured into 150 ml. of water; no lead dioxide was obtained. Potassium hydroxide (50 g.) was added to the solution and the mixture was extracted with ether. The ether solution was washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated using a rotary evaporator to give 9.3 g. of crude product. Distillation gave 3.8 g. of recovered reactant, 2.0 g. of monoacetates (b.p. 110–118°), and 3.2 g. of higher boiling residue which was largely diacetates. The monoacetate fraction was shown by gas chromatography to contain 6.4% reactant and 48% (17% yield) carvotanacetol acetates with an isomer ratio of 60% trans to 40% cis.

Reaction of 1-Methylcyclohexene with Lead Tetraacetate.— The reaction of 2.4 g. (25 mmoles) of 1-methylcyclohexene with 10.8 g. (24.4 mmoles) of lead tetraacetate in 50 ml. of benzene was carried out as described above. Distillation of the reaction product gave 0.9 g. (24%) of 6-acetoxy-1-methylcyclohexene, b.p. 70-75° at 10 mm.

Competitive Oxidation of Cyclohexene and 1-Methylcyclohexene with Lead Tetraacetate.—A mixture of 8.9 g. (20 mmoles) of lead tetraacetate, 1.62 g. (20 mmoles) of cyclohexene, 1.94 g. (20 mmoles) of 1-methylcyclohexene, and 50 ml. of benzene was heated to reflux for 14 hr. The reaction mixture was worked up as described above giving 1.2 g. of acetates, b.p. 70–85° at 15 mm. Gas chromatography indicated the presence of 6-acetoxy-1-methylcyclohexene and 3-acetoxycyclohexene in ratio of 71:29.

Oxidation of Cyclohexene-1-C¹³ with Lead Tetraacetate.— The oxidations were carried out using both acetic acid and benzene as solvents and the procedure described above. Using benzene, 28% of 3-acetoxycyclohexene was obtained, and, using acetic acid, 22% of 3-acetoxycyclohexene was found. After hydrolysis and chromic acid oxidation as described above, the cyclohexanone was degraded using the procedure of Loftfield, and the carbon dioxide formed was analyzed mass spectrometrically.

Selenium Dioxide Oxidation of (+)-Carvomenthene in Ethanol. —To 11.5 g. (83.6 mmoles) of (+)-carvomenthene, αD +91.7°, in 15 ml. of 95% ethanol, which was stirred at reflux, was added dropwise over a period of 5 hr. 9.3 g. (84 mmoles) of selenium dioxide in 50 ml. of 95% ethanol. The mixture was heated to reflux for an additional 15 hr. The reaction mixture was cooled and filtered giving 5.5 g. (83%) of selenium. The filtrate was distilled at reduced pressure to remove most of the solvent, and the residue was steam distilled. The distillate was extracted twice with ether. The combined ether solution was washed with water, dried over anhydrous sodium sulfate, and concentrated using a rotary evaporator. The residue was distilled giving 9.7 g. of crude product, b.p. 100–140°, at 13 mm., and 1.0 g. of residue.

The crude product was analyzed by gas chromatography and was found to contain 7.2 g. (75%) of (+)-carvotanacetone (α D +28.6°), 1.0 g. (10%) of (+)-phellandral, (α D +117.4°), and 1.3 g. (14%) of an unsaturated hydrocarbon.

Reaction of Selenium Dioxide with Excess (+)-**Carvomenthene** in Acetic Acid.—To a solution of 8.0 g. (58 mmoles) of (+)-carvomenthene, αp +89.4°, in 30 ml. of glacial acetic acid and 10 ml. of acetic anhydride was added 1.97 g. (17.7 mmoles) of selenium dioxide. The mixture was heated with stirring on a steam bath for 8 hr. The precipitated selenium (0.9 g., 71%) was removed by filtration, and the filtrate was steam distilled. The distillate was extracted twice with ether. The ether solution was washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated using a rotary evaporator. Distillation of the residue gave 2.8 g. of starting material, αp +89.8°, and 3.9 g. of acetates, b.p. 108–118° at 10 mm. Analysis of the latter by gas chromatography indicated the presence of 53% (30% yield) of carvotanacetol acetates with an isomer ratio of 61% trans to 39% cis. Reaction of Cyclohexene-1-C¹³ with Selenium Dioxide in Acetic Acid.—To a solution of 4.05 g. (49 mmoles) of cyclohexene-1-C¹³ in 50 ml. of glacial acetic acid and 5 ml. of acetic anhydride was added 2.70 g. (24.5 mmoles) of selenium dioxide, and the mixture was heated on a steam bath with stirring overnight. The solution was filtered to remove selenium (0.24 g., 12%) and the filtrate was steam distilled. Essentially, no oxidized material was found in the distillate.

The residue from the steam distillation was taken up in ether. The ether solution was dried over anhydrous sodium sulfate and concentrated using a rotary evaporator giving 2.2 g. of residue. Pyrolysis carried out in a distilling flask, gave 1.34 g. of essentially pure 3-acetoxycyclohexene. This was degraded in the manner described above.

Chromic Acid Oxidation of Cyclohexene-1-C¹³.—To a solution of 4.1 g. of cyclohexene in 10 ml. of acetic acid was added with stirring at room temperature a solution of 7.5 g. of chromium trioxide in 4.5 ml. of water and 15 ml. of acetic acid over a period of 7 hr. After an additional hour, the solution was distilled giving 1.9 ml. of recovered cyclohexene. A solution of 12 g. of sodium hydroxide in 12 ml. of water was added to the remaining acetic acid solution with external cooling. The gelatinous mixture was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and distilled giving cyclohexenone, b.p. $69-71^{\circ}$ at 20 mm. After hydrogenation, the cyclohexanone was degraded by the method of Loftfield.¹⁴

A Synthesis of Iridomyrmecin

Keiiti Sisido, Kiitirô Utimoto, and Tyûzô Isida

Department of Industrial Chemistry, Kyôto University, Kyoto, Japan

Received April 16, 1964

Hydroboration of ethyl 2-(3-methyl-2-methylenecyclopentyl)propionate (V) followed by oxidation gave a mixture of *dl*-iridomyrmecin (IX) and *dl*-isoiridomyrmecin in satisfactory yield. The ester V was obtained from ethyl 2-(3-methyl-2-oxocyclopentyl)propionate (IV) by the Wittig reaction with methylenetriphenylphosphorane. The Darzens-Claisen glycidic ester condensation of IV did not give 2-(2-formyl-3-methylcyclopentyl)propionic acid. This formyl derivative was obtained by condensation of IV with methoxymethylenetriphenylphosphorane followed by hydrolysis. However, reduction of the carbonyl group gave the *trans*-lactone, an isomer of iridomyrmecin.

In continuation of the interest in preparative studies on natural cyclopentane derivatives,¹ a synthesis of iridomyrmecin was effected. This bactericidal and insecticidal lactone of an Argentine ant, *Iridomyrmex humilis*,^{2,3} was found also to be a cat-attracting ingredient of a Japanese plant *Actinidia polygama* Miq.⁴

The reported syntheses of iridomyrmecin and isoiridomyrmecin⁵ consisted in either an intramolecular cyclization of an acyclic C_{10} compound⁶ or an addition of a side chain to cyclopentene derivatives.⁷ The present investigation started from a cyclopentanone derivative, ethyl 2-(3-methyl-2-oxocyclopentyl)propionate (IV).⁸

- (2) M. Pavan, Proc. Intern. Congr. Entomol., 8th, Stockholm, 1948, 863
 (1950); Chem. Abstr., 45, 9809b (1951); Ric. sci., 19, 1011 (1949); Chem. Abstr., 45, 7309a (1951); Chim. ind. (Milan), 37, 714 (1955); Chem. Abstr., 50, 13311c (1956).
- (3) R. Fusco, R. Trave, and A. Vercellone, Chim. ind. (Milan), **37**, 251 (1955); Chem. Abstr., **50**, 8451f (1956).

(4) (a) T. Sakan, A. Fujino, F. Murai, A. Suzui, and Y. Butsugan, Bull. Chem. Soc. Japan, 32, 1154 (1959); Chem. Abstr., 54, 18492b (1960); (b)
T. Sakan, A. Fujino, and F. Murai, Nippon Kagaku Zasshi, 81, 1320, 1324 (1960); Chem. Abstr., 56, 11644b, 11644c (1962).

(5) (a) G. W. K. Cavill, D. L. Ford, and H. D. Locksley, Chem. Ind. (London), 465 (1956); Australian J. Chem., 9, 288 (1956); (b) G. W. K. Cavill and H. D. Locksley, *ibid.*, 10, 352 (1957).

(6) K. J. Clark, G. I. Fray, R. H. Jaever, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

(7) (a) F. Korte, J. Falbe, and A. Zschocke, *ibid.*, **6**, 201 (1959); (b) F. Korte, K. H. Büchel, and A. Zschocke, *Chem. Ber.*, **94**, 1952 (1961).

(8) R. P. Linstead and R. L. Jones, J. Chem. Soc., 616 (1936).

An improved preparation⁹ of 2-carbethoxy-5-methylcyclopentanone (I)¹⁰ from 2-carbethoxy-2-methylcyclopentanone¹⁰⁻¹² allowed the subsequent reactions without isolating the intermediates. Addition of ethyl 2bromopropionate to the reaction product followed by hydrolysis, decarboxylation, and esterification gave IV in 55% yield.



The acetoacetic ester synthesis applied to I is believed to afford *trans*-2,5-disubstituted cyclopentanone III.

- (9) K. Sisido, K. Utimoto, and T. Isida, J. Org. Chem., 29, 2781 (1964).
- (10) L. Bouveault and R. Locquin, Bull. soc. chim. France, [4] 3, 441 (1908).
- (11) F. H. Case and E. E. Reid, J. Am. Chem. Soc., 50, 3026 (1928).
- (12) L. Nicole and L. Berlinguet, Can. J. Chem., 40, 353 (1962).

⁽¹⁾ K. Sisido, S. Torii, and M. Kawanisi, J. Org. Chem., 29, 904 (1964): 29, 2290 (1964).